Single-Drop Microextraction

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Abstract Since its discovery in 1995 by Dasgupta et al., and further implementation by Jeannot et al. in 1996, single-drop microextraction (SDME) has undergone a dramatic increase, as demonstrated by the significant number of developments and the plethora of applications that have extended this technique to almost every area, being nowadays one of the most popular miniaturised extraction techniques. The diversity of analytes, possibilities of combining SDME to detection techniques, the continuous improvements in extractant phases and the simplicity of operation, account for the spread acceptance of SDME. In this chapter, the different approaches available under the concept of extraction in a drop, extractant phases, both conventional and novel ones, as well as couplings of SDME with different detectors will be addressed. Relevant applications of SDME will be provided emphasizing analytical characteristics such as detection limits, precision and enrichment factors. Apart from the well-established modes of SDME such as direct immersion single-drop microextraction (DI-SDME), directly suspended drop microextraction (DSDME), headspace single-drop microextraction (HS-SDME), continuous flow microextraction (CFME) and liquid–liquid-liquid microextraction (LLLME), novel sophisticated approaches have arisen in the last years, such as drop-to-drop solvent microextraction (DDSME) or bubble-in-drop microextraction (BID), which provide new avenues for the continuous improvement of this technique.

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Abbreviations

AFS	Atomic fluorescence spectrometry
Ag@Au np	Silver-gold core–shell nanoprisms
APDC	Ammonium pyrrolidinedithiocarbamate
APIs	Active pharmaceutical ingredients
ATR-FTIR	Attenuated total reflectance-Fourier transform infrared spectroscopy
Au-np/TR	Gold nanoprisms/Tollen's reagent
BID	Bubble-in-drop
BPHA	N-benzoyl-N-phenylhydroxylamine
BTEXs	Benzene, toluene, ethylbenzene and xylenes
CCU-CF-SDME	Column clean-up continuous flow single-drop microextraction
CDs	Carbon dots
CE	Capillary electrophoresis
CE-MS	Capillary electrophoresis mass spectrometry
CE-UV	Capillary electrophoresis ultra-violet detector
CFME	Continuous flow microextraction
CV	Cold vapour
CZE	Capillary zone electrophoresis
DDSME	Drop-to-drop solvent microextraction
DES	Deep eutectic solvent
DI-SDME	Direct immersion single-drop microextraction
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DRS-FTIR	Diffuse reflectance-Fourier transform infrared spectroscopy
DSDME	Directly suspended droplet microextraction
DS-LLLME	Directly suspended liquid–liquid-liquid microextraction
ECD	Electron capture detector
EDXRF	Energy dispersive X-ray fluorescence
EF	Enrichment factor
ESI	Electrospray ionization
ETAAS	Electrothermal atomic absorption spectrometry
ETV	Electrothermal vaporisation
ETV-ICP-MS	Electrothermal vaporisation inductively coupled plasma mass spectrometry
FAAS	Flame atomic absorption spectrometry
FID	Flame ionization detector

GC	Gas chromatography
GC-ECD	Gas chromatography electron capture detector
GC-FID	Gas chromatography flame ionization detector
GC–MS/MS	Gas chromatography-tandem mass spectrometry
GC–MS	Gas chromatography mass spectrometry
GF	Graphite furnace
GF-AAS	Graphite furnace atomic absorption spectroscopy
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HG	Hydride generation
HPLC	High performance liquid chromatography
HPLC–DAD	High performance liquid chromatography photodiode array detector
HPLC–UV	High performance liquid chromatography ultra-violet detector
HS-BID	Headspace bubble-in-drop
HS-SDME	Headspace single-drop microextraction
HS-SDME-SP	Headspace single-drop microextraction spectro-pipette
HTL	Homocysteine thiolactone
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
ILs	Ionic liquids
IMS	Ion-mobility spectrometry
IR	Infrared
LC	Liquid chromatography
LC–MS/MS	Liquid chromatography tandem mass spectrometry
LGL	Liquid–gas-liquid
LIBS	Laser-induced breakdown spectroscopy
LIS	Lab-in-syringe
LLE	Liquid–liquid extraction
LLL	Liquid–liquid-liquid
LLLME	Liquid–liquid-liquid microextraction
LLL-SDME	Liquid–liquid-liquid single-drop microextraction
LOD	Limit of detection
LPME	Liquid phase microextraction
MALDI	Matrix-assisted laser desorption/ionization
MALDI-MS	Matrix-assisted laser desorption/ionization mass spectrometry
MALDI-TOF-MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MBGs	Magnetic bucky gels
mCNTs	Magnetic-carbon nanotubes
MIL	Magnetic ionic liquid
MS	Mass spectrometry

MTME-SD	Magnetic tip microextraction to a single drop
MTP-SDME	Magnetic three phase single-drop microextraction
NCs	Nanoclusters
N-GQDs	Nitrogen-doped graphene quantum dots
NPs	Nanoparticles
NRs	Nanorods
NSAIDs	Non-steroidal anti-inflammatory drugs
NSRs	Nanostars
NTs/G-quadruplex/PPIX	Nanosheets G-quadruplex/protoporphyrin IX
PAHs	Polycyclic aromatic hydrocarbons
PAN	1-(2-Pyridylazo)-2-naphtol
Pa-SDME	Parallel single-drop microextraction
PBDEs	Polybrominated diphenyl ethers
PMAA	Poly(metacrylic acid)
pMBA	Para-mercaptobenzoic acid
PS-MS	Paper spray mass spectrometry
PTLM	Photothermal lens microscopy
PTV	Programmable temperature vaporisation
QDs	Quantum dots
qPCR	Quantitative polymerase chain reaction
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RSD	Relative standard deviation
RTGC	Room temperature gas chromatography
RTGC-IMS	Room temperature gas chromatography ion-mobility spectrometry
SDILNDμE	Single-drop ionic liquid non-dispersive microextraction
SDME	Single-drop microextraction
SDME-GC	Single-drop microextraction gas chromatography
SDME-LVSEP	Single-drop microextraction large-volume sample stacking electroosmotic flow pump
SDS	Sodium dodecyl sulphate
SENLIBS	Surface-enhanced laser-induced breakdown spectroscopy
SERS	Surface-enhanced Raman scattering
SFODME	Solidified floating organic drop microextraction
SI	Sequential injection
SUPRADES	Supramolecular deep eutectic solvent
SUPRAS	Supramolecular solvent
TOF	Time-of-fligth
TXRF	Total reflection X-ray fluorescence
UHPLC-MS/MS	Ultra-high performance liquid chromatography tandem mass spectrometry

1 Introduction

Sample preparation represents a key step of the analytical process in most analytical methodologies. Particularly, extraction techniques such as solid-phase extraction and solvent extraction have been typically employed for achieving the extraction and enrichment of target analytes, an efficient sample clean-up and/or to obtain an extract compatible with the analytical instrumentation. However, these conventional extraction techniques are not free from drawbacks, including the achievement of reduced enrichment factors, a large consumption of solvents and, thus, generation of wastes, apart from the tendency to form undesirable emulsions that impair the separation of phases in solvent extraction. The main limitations of these classical techniques led to the development of miniaturised extraction counterparts, commonly termed as microextraction techniques. Since their introduction in the mid-1990s as a consequence of very remarkable disruptive works [1–4], substantial efforts have been made for the development of convenient and complementary microextraction approaches. Thus, a wide range of single drop microextraction (SDME) modes can nowadays be selected for (virtually) solving any analytical problem.

The chapter provides an overview of the inception and evolution of SDME, highlighting the main achievements and applications of the technique, paying special attention to fundamental thermodynamic and kinetic aspects. The chapter focuses on liquid-phase microextraction (LPME) approaches involving microdrops of extractant phases in a nearly spherical configuration during the extraction process and, therefore, related LPME approaches that do not fulfil this criterion, such as dispersive liquid–liquid microextraction or LPME approaches involving supported liquid membranes, among others, can be found in Chaps. 8, 9 and 10 of this book. Recent review articles dealing with these contents can also be found elsewhere [5, 6].

2 Fundamentals

In this section, the most prominent SDME approaches are presented and theoretical aspects of two-phase and three-phase SDME systems are provided.

2.1 SDME Approaches

A number of SDME approaches, involving both two-phase and three-phase systems, have been reported in the literature. A schematic representation of SDME approaches described below is shown in Fig. 1.

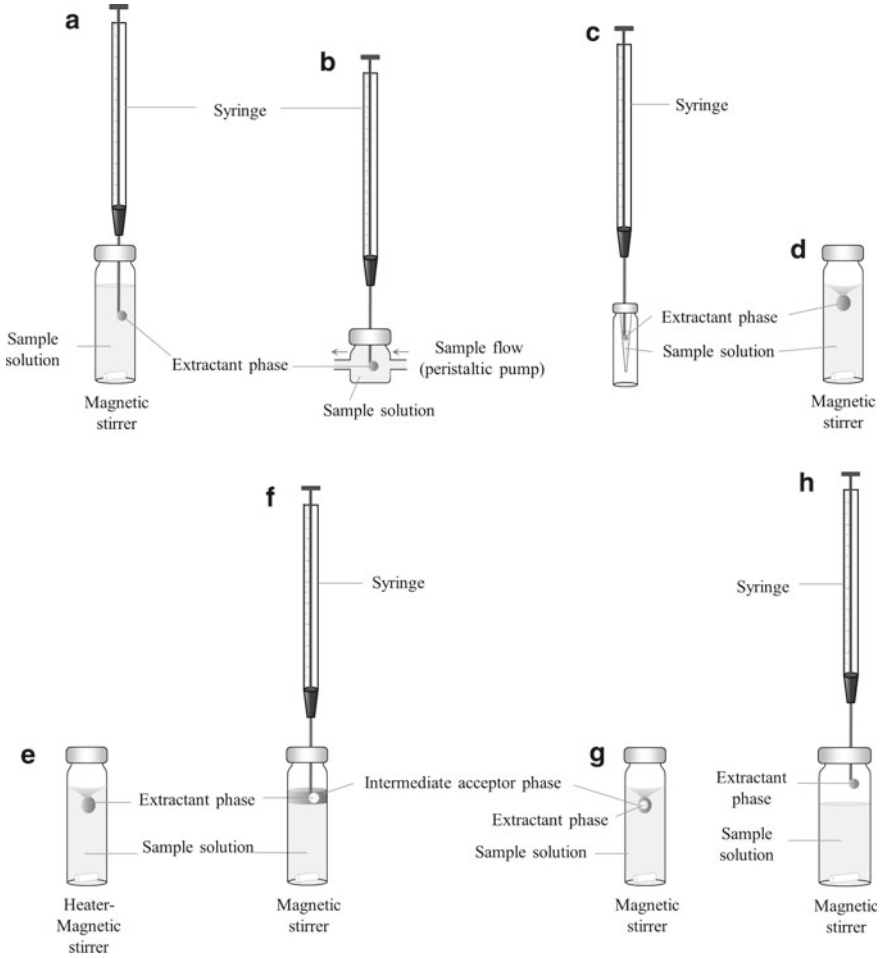

Fig. 1 Schematic representation of SDME approaches. DI-SDME **a**, CFME **b**, DDSDME **c**, DSDME **d**, SFODME **e**, LLLME **f**, DSLLLME **g** and HS-SDME **h**

2.1.1 Two-Phase SDME Approaches

Biphasic systems can be considered as purely miniaturised solvent extraction approaches, involving the direct exposure of a microdrop of immiscible extractant phase to an aqueous sample. Biphasic SDME has been mainly used with the aim of extracting target analytes (or analyte derivatives) displaying moderate to high hydrophobicity. The basic requirements of solvents to be used in two-phase SDME include immiscibility with the sample and highly reduced solubility on the aqueous phase. The first attempts to miniaturise the conventional solvent extraction reported on the exposure of a microdrop of immiscible organic solvent hanging from the tip of a capillary to an aqueous sample [4, 7], even though the use of a microsyringe

was soon found to be highly convenient to facilitate the reproducible exposure of a microvolume of extractant phase, followed by the retraction and injection of the enriched extractant phase for analysis [8]. From these first studies, different biphasic SDME approaches have been reported in the literature. In direct (or immersed) SDME (DI-SDME, Fig. 1a), the microdrop of extractant phase is immersed in the sample (typically 1–2 cm below the surface of the aqueous sample solution) hanging from the tip of a microsyringe. Convection is commonly favoured to enhance the extraction kinetics, mainly by magnetic stirring or sample pumping. In the second case, the SDME mode is commonly termed as continuous flow microextraction (CFME, Fig. 1b) [9]. Furthermore, a highly miniaturised approach, particularly suitable for the enrichment of target compounds present in limited sample volumes (*e.g.*, clinical samples) named as drop-to-drop solvent microextraction (DDSME, Fig. 1c) has been reported [10], in analogy to a previous approach described by Dasgupta et al. in the mid-90s [7]. In spite of the convenience of using a microsyringe to integrate unitary steps, the performance of these biphasic SDME approaches is severely limited by the instability of the microdrop under certain experimental conditions. Particularly, extended extraction times, high agitation or relatively high temperatures, which generally lead to enhanced extraction, affected the balance of forces on the microdrop, leading to drop dislodgement. Thus, alternative biphasic SDME approaches that do not make use of the syringe as a holder but to collect the enriched microdrop at the end of the process have been reported to overcome the above limitations, namely directly suspended droplet microextraction (DSDME) and solidification floating organic drop microextraction (SFODME). In DSDME (Fig. 1d), a microvolume of an immiscible extractant phase showing lower density than water is directly injected at the top of a highly stirred aqueous sample, thus forming a self-stable drop that maintains a nearly spherical configuration during the extraction process. The fact that the extractant phase is freely suspended in the sample allows the use of very high stirring rates, which favours the extraction kinetics. On the other hand, however, the collection of the enriched microdrop at the end of the process becomes more complicated with regard to SDME modes that make use of the syringe as a holder of the microdrop. Different options have been considered to facilitate the collection stage immediately prior to analysis, including the design of collection devices with narrow-neck tubes [11] or the use of syringes for improved extraction with subsequent collection of the enriched acceptor phase at its tip [12]. In addition, the introduction of an analogous biphasic SDME approach, namely SFODME (Fig. 1e) [13], has also simplified the collection step. SFODME exploits the physicochemical properties of certain solvents used as extractant phases to induce their physical separation after the enrichment process. In particular, apart from being immiscible with water and showing lower density that water, the solvents used as extractant phases in SFODME must fulfil the additional requirement of showing a melting point close to room temperature (*ca.* 10–30 °C). Thus, the process of analyte extraction from the sample solution is carried out in an analogous way to DSDME but at a temperature higher than the melting point of the extractant phase to maintain it in its liquid phase during the extraction process (commonly requiring a thermostatic bath). The collection of the enriched drop is performed at lower temperature than the melting point by locating the vial in

an ice bath, that leads to the solidification of the drop, thus facilitating the collection of the enriched solid-microdrop by using a spatula or tweezers. Then, the enriched solvent melts immediately before analysis. The numerous requirements that must be met by potential extractant phases significantly limit their choice to a reduced set of solvents whose properties might not comply with the principle of "like dissolves like".

2.1.2 Three-Phase SDME Approaches

Three-phase systems have been reported for enhanced selectivity. Thus, liquid–liquid-liquid microextraction systems (LLLME) and headspace SDME (HS-SDME) have been reported in the literature for the enrichment of ionisable and volatile (or semivolatile) compounds, respectively. These three-phase SDME approaches involve liquid–liquid-liquid and liquid–gas-liquid mass transfer processes, respectively.

In LLLME, a reduced volume of an immiscible solvent showing lower density than water is layered over a stirred aqueous sample and, in turn, a microdrop of extractant phase (by default of aqueous nature) is immersed into the intermediate acceptor phase. The exposure of the extractant phase can be carried out by using a syringe as holder during the microextraction process (Fig. 1f) or by delivering the extractant phase microdrop in the intermediate acceptor phase (Fig. 1g), in the so called directly suspended three phase liquid phase microextraction (DS-LLLME). In the latter case, the syringe is not used as a holder during the extraction process but to collect the enriched microdrop for analysis. Simultaneous extraction (from the sample to the intermediate acceptor phase, equivalent to DI-SDME) and back-extraction (from the intermediate acceptor phase to the extractant phase microdrop) of target analytes occur in LLLME and DS-LLLME. Careful adjustment of the pH of both the aqueous sample and the extractant phase bearing in mind the pKa values of target analytes is mandatory for achieving an efficient extraction of target analytes. In particular, ionisable compounds must be in their neutral form to be extracted by the intermediate organic layer, whereas ionisation of the analyte must occur at the interface organic layer-aqueous receiving phase to favour the back-extraction into the aqueous extractant phase. By way of example, the LLLME of amines present in an aqueous sample required the pH adjustment of the sample solution and the aqueous microdrop at alkaline and acidic values, respectively [14]. Furthermore, the use of chelating agents in the extractant phase has expanded the applicability of LLLME for the extraction of metal ions and organometallic compounds [15, 16].

An alternative three-phase SDME mode, named as HS-SDME, is widely used for the enrichment of volatile compounds present in condensed samples [17]. HS-SDME is based on the extraction of analytes (or analyte derivatives) by a microdrop of extractant phase exposed to the headspace above a sample, in a closed vial (Fig. 1h). Volatile and semi-volatile compounds are thus transferred from the sample solution to the gaseous phase above it and subsequently extracted by the extractant phase microdrop when the "like dissolves like" principle is met. Apart from showing appropriate partition coefficients to ensure an efficient retention of target molecules, the

extractant phases should show a reduced vapour pressure and relatively high boiling point. Obviously, the immiscibility of the solvent with the sample is not relevant in HS-SDME since these phases are not in contact with each other during the extraction process. Magnetic agitation is typically employed for efficiently transfer the volatile to the gaseous phase, even though increased temperatures and/or increase of the ionic strength can also be required to improve the process.

In comparison with biphasic systems, the selectivity of three-phase SDME approaches is highly increased bearing in mind that the extractant phase is physically separated (by an intermediate immiscible liquid phase or a gaseous phase) from the sample solution. Thus, potential interferences associated with certain compounds present in the sample can be avoided or minimised. For instance, the extraction of non-ionisable compounds by the extractant phase microdrop is avoided in liquid–liquid-liquid (LLL) approaches, even if they are extracted by the intermediate solvent phase. Analogously, non-volatile compounds present in aqueous samples cannot be transferred to the headspace and therefore their extraction by a microdrop exposed to the gaseous phase is not produced.

2.2 Theoretical Aspects of SDME

2.2.1 Thermodynamics of SDME

In SDME modes involving two phases, *i.e.*, aqueous sample and microdrop of extractant phase, the distribution constant, K_{ds}, can be expressed as the ratio of activities of the analytes in the drop of extractant phase and the sample. Bearing in mind that analytes are commonly present at trace and ultratrace levels, activities can be approximated by the corresponding concentrations:

$$K_{ds} = \frac{a_d}{a_s} \approx \frac{C_d}{C_s} \tag{1}$$

where a_d and a_s are the activities of the analytes in the extractant drop phase and sample, respectively, and C_d and C_s are the corresponding concentrations of the analytes in the extractant drop phase and sample, respectively.

Under equilibrium conditions, the amount of analyte present in the extractant phase, n_d, can be expressed as shown in Eq. (2), regardless the number of phases involved in the SDME process:

$$n_d = \frac{K_{ds} V_d C_0 V_s}{K_{ds} V_d + K_{hs} V_h + V_s} \tag{2}$$

where C_0 is the initial concentration of the analyte in the sample, V_s, V_h and V_d are the sample, headspace and drop volumes, respectively, and K_{ds} and K_{hs} are the drop/sample and headspace/sample distribution constants, respectively. It should be noted

that the term $K_{hs}V_h$ present in the denominator of Eq. (2) is omitted when two-phase SDME modes are used. It is worth mentioning that the Eq. (2) can be simplified as shown in Eq. (3) when $V_s \gg V_d$ (and $V_s \gg V_h$, if applicable):

$$n_d = K_{ds}V_dC_0 \tag{3}$$

According to this expression, the amount of analyte extracted is independent on the sample volume when the above conditions are fulfilled. This aspect is of particular importance since it would (ideally) allow integrating sampling and sample preparation without significant modifications on the extracted amount of analytes when very large sample volumes are involved.

The expression for the concentration of the analyte in the extractant phase under equilibrium conditions in two-phase SDME approaches, in which a single equilibrium is involved, can be directly deduced from Eq. (2), being equivalent to the one valid for conventional liquid–liquid extraction (LLE):

$$C_d = \frac{K_{ds}C_0}{1 + K_{ds}\left(\frac{V_d}{V_s}\right)} \tag{4}$$

Two additional expressions can be deduced for the concentration of the analyte in the extractant phase under equilibrium conditions of three-phase SDME approaches. Two equilibria are involved in LLL and liquid–gas-liquid (LGL) microextraction processes, respectively.

In LLLME approaches, the concentration of the analyte in the extractant phase under equilibrium conditions can be expressed as:

$$C_d = \frac{K_{ds}C_0}{1 + K_{as}\left(\frac{V_a}{V_s}\right) + K_{ds}\left(\frac{V_d}{V_s}\right)} \tag{5}$$

where K_{as} is the intermediate acceptor phase/sample distribution constant and V_a is the corresponding volume.

Analogously, in the headspace mode, the concentration of the analyte in the extractant phase under equilibrium conditions can be estimated as:

$$C_d = \frac{K_{ds}C_0}{1 + K_{hs}\left(\frac{V_h}{V_s}\right) + K_{ds}\left(\frac{V_d}{V_s}\right)} \tag{6}$$

2.2.2 Kinetics of SDME

Two-Phase SDME Approaches

It has been experimentally verified that a first-order kinetic model fits well with the experimental data of concentration of the analyte in the extractant phase *vs* time, t, with both two and three-phase SDME approaches [4, 17, 18]:

$$C_d = C_d^{eq}\left(1 - e^{-kt}\right) \tag{7}$$

where C_d^{eq} corresponds to the concentration of the analyte in the extractant phase under equilibrium conditions and k is the observed rate constant.

The complexity of the observed rate constant, k, depends on a high extent on the number of phases involved. The Eq. (8) shows the expression reported in the literature for two-phase SDME modes [4]:

$$k = \frac{A_{ds}}{V_d}\overline{\beta}_d\left(1 + K_{ds}\frac{V_d}{V_s}\right) \tag{8}$$

where A_{ds} is the interfacial area and $\overline{\beta}_d$ is the overall mass transfer coefficient with respect to the extractant phase, which can be expressed as follows assuming rapid transfer across the liquid–liquid interface:

$$\frac{1}{\overline{\beta}_d} = \frac{1}{\beta_d} + \frac{K_{ds}}{\beta_s} \tag{9}$$

where β_d and β_s are the individual mass transfer coefficients for the extractant phase and sample, respectively.

The above expression can be written according to the film theory, which assumes that steady-state diffusion occurs from one phase (sample) to another (extractant phase) through stagnant layers (named as Nernst diffusion films) of thicknesses δ_d and δ_s adjacent to the interface in the extractant phase and sample, respectively, as follows:

$$\frac{1}{\overline{\beta}_d} = \frac{\delta_d}{D_d} + \frac{K_{ds}\delta_s}{D_s} \tag{10}$$

where D_d and D_s are the corresponding diffusion coefficients of the analyte.

The impact of experimental parameters on the extraction kinetics can be deduced from Eq. (10). Accordingly, rapid extraction can be attained when maximizing A_i, β_d and β_s, while minimizing V_s for a given combination of target analyte and extractant phase, which in turn defines K_{ds}. An efficient agitation reduces the thicknesses of stagnant layers and increases the mass transfer coefficients and, thus, the extraction kinetics. In fact, a log–log relationship between $\overline{\beta}_d$ and the stirring rate has been verified in two phases SDME approaches [4].

Three-Phase SDME Approaches

An expression for the time dependence of the analyte concentration extracted by a microdrop in a three-phase LLLME approach, has been given by the following equation [18]:

$$C_d = C_0\left(\frac{V_s}{V_d}\right)\left\{\frac{k_1k_3}{\lambda_1\lambda_3} + \frac{k_1k_3}{\lambda_2(\lambda_2-\lambda_3)}e^{-\lambda_2 t} + \frac{k_1k_3}{\lambda_3(\lambda_2-\lambda_3)}e^{-\lambda_3 t}\right\} \tag{11}$$

where λ_2 and λ_3 correspond to:

$$\lambda_2 = \frac{1}{2}\left\{(k_1+k_2+k_3+k_4) + \left[(k_1+k_2+k_3+k_4)^2 - 4(k_1k_3+k_2k_4+k_1k_4)\right]^{1/2}\right\} \tag{12}$$

$$\lambda_3 = \frac{1}{2}\left\{(k_1+k_2+k_3+k_4) - \left[(k_1+k_2+k_3+k_4)^2 - 4(k_1k_3+k_2k_4+k_1k_4)\right]^{1/2}\right\} \tag{13}$$

In addition, the first-order rate constant k depends on the individual rate constants as follows when the steady-state approximation is assumed [14]:

$$k \approx \frac{k_1k_3}{k_2+k_3} \tag{14}$$

Under these conditions, k can be expressed as:

$$k = \frac{A_{da}A_{as}K_{as}\overline{\beta}_{as}\overline{\beta}_{da}}{V_s\left(A_{da}K_{da}\overline{\beta}_{as} + A_{as}\overline{\beta}_{da}\right)} \tag{15}$$

It can be inferred from this expression that the extraction kinetics in three-phase LLLME approaches is enhanced by an increase on the intermediate acceptor phase/sample distribution ratio, K_{as}, the interfacial areas involved, A_{da} and A_{as}, and the mass transfer coefficients, $\overline{\beta}_{as}$ and $\overline{\beta}_{da}$, as well as a decrease on the sample volume, V_s. Efficient agitation of the sample favours the mass transfer across the sample-intermediate acceptor phase and, in turn, induces convection in the intermediate immiscible phase. Thus, the thicknesses of the four Nernst diffusion films involved in the process are decreased and the mass transfer coefficients increased.

A kinetic model for HS-SDME has also been reported by assuming "steady-state approximations" [19]. Accordingly, Eq. (7) has been deduced as a valid expression for the time dependence of the analyte concentration in the microdrop exposed to the headspace above the sample, where the rate constant k is expressed as:

$$k = \frac{A_{dh}A_{hs}\overline{\beta}_{dh}\overline{\beta}_{hs}}{V_d\left(A_{dh}\overline{\beta}_{dh}K_{dh} + A_{hs}\overline{\beta}_{hs}\right)}\left(K_{ds}\frac{V_d}{V_s} + 1\right) \tag{16}$$

$\overline{\beta}_{dh}$ and $\overline{\beta}_{hs}$ can be expressed as a function of each mass transfer coefficient and the corresponding distribution constants:

$$\overline{\beta}_{dh} = \frac{\beta_{dh}\beta_d}{\beta_{dh} + K_{dh}\beta_d} \tag{17}$$

$$\overline{\beta}_{hs} = \frac{\beta_s\beta_{hs}}{\beta_s + K_{hs}\beta_{hs}} \tag{18}$$

where β_s, β_{hs}, β_{dh} and β_d are the mass transfer coefficients for the aqueous sample, headspace by water sample, extractant phase by headspace and extractant phase, respectively.

On a general basis, mass transfer into the microdrop represents a slow step due to its purely diffusive nature, as reported in the literature [17]. In addition, mass transfer in the aqueous sample is also slow and represents another limiting step in the extraction process. Thus, the above Eqs. (17) and (18) can be simplified to β_d and β_s/K_{hs}, respectively, assuming that the mass transfer in the condensed phases are the limiting steps. Accordingly, Eq. (16) can be simplified as:

$$k = \frac{A_{dh}A_{hs}\beta_d\beta_s}{V_d K_{hs}\left(A_{dh}\beta_d K_{dh} + A_{hs}\left(\frac{\beta_s}{K_{hs}}\right)\right)}\left(K_{ds}\frac{V_d}{V_s} + 1\right) \tag{19}$$

This equation is particularly valid for highly volatile analytes. Regarding less volatile compounds, the Eq. (19) can be simplified further since K_{hs} is very small and, therefore, it can be assumed that $A_{hs}\beta_s/K_{hs} \gg A_{dh}\beta_d K_{dh}$. Under these conditions, the expression for the rate constant can be simplified to:

$$k \approx \frac{A_{dh}\beta_d}{V_d}\left(K_{ds}\frac{V_d}{V_s} + 1\right) \tag{20}$$

It can be deduced from this equation that diffusion into the extractant phase microdrop is the rate limiting step in the extraction of less volatile analytes.

As discussed above, the rate-limiting steps of the process can correspond to the mass transfer in both condensed phases, namely the extractant phase and the aqueous sample. Agitation of the sample favours the mass transfer and induces convection in the headspace. Diffusion coefficients in the gaseous phase are four orders of magnitude higher than in condensed phases and, therefore, mass transfer in the headspace has been typically considered a fast process. Recent contributions, however, have revealed that interfacial gas-phase constraints are non-negligible, affecting both the evaporation and uptake, and can be significantly minimised under reduced sampling pressures [20].

3 Novel Developments

The evolution of SDME modes in chronological order is presented in Sect. 3.1, describing advantages, limitations and requirements, as well as recent developments. In addition, relevant information on the extractant phases used in SDME is described in Sect. 3.2, paying special attention to neoteric solvents. Furthermore, coupling of SDME to different analytical instruments, including their improvements via automation, is discussed in Sect. 3.3.

3.1 Evolution of SDME Modes: Main Achievements

The first SDME-related works were reported in 1995. In these contributions, aqueous droplets containing colorimetric reagents showed much potential for trapping NH_3, SO_2 [3] and Cl_2 [2] gases from air samples. The miniaturisation of conventional LLE occurred one year later, with two works based on the exposure of a microdrop hanging from the tip of a capillary tube to aqueous phases [4, 7]. Thus, the direct immersion mode was exploited for extraction of 4-methylacetophenone in a small drop of n-octane (immiscible in sample aqueous solution) [4], whereas an organic drop placed in a flowing aqueous sample enabled the determination of sodium dodecyl sulphate [7].

Capillary tubes initially used as holders of the extractant phase were then replaced by chromatography syringes, which simplified the process by integration of unitary steps [8]. In fact, the microsyringe was found to be suitable for both holding the solvent drop during extraction and facilitating the drop introduction into the instrument.

General advantages of SDME include the use of a very small volume of organic solvent, and the absence of sample carryover or memory effects due to the solvent renovation for each extraction. However, the small volume of solvent drops prevents the possibility to perform measurement replicates. Different SDME modes were sequentially introduced to solve several inconveniences found during their application, such as extended extraction times and high temperatures, and drop instability (or even drop detachment) in two phase-SDME modes, especially at high stirring rates.

A three-phase SDME mode, namely LLLME, was introduced in 1998 [14]. LLLME involves two consecutive extractions, typically from aqueous sample to an organic donor phase and then, to an aqueous acceptor drop. LLLME was firstly applied using a Teflon ring to place the octane phase between the two aqueous phases, and evolved a year later to potentially improve the enrichment factors by reducing the volume of the extractant phase [14]. Usually, the extractant phase microdrop is immersed on the second phase (*e.g.*, 100 μL of organic solvent) which floats over the aqueous sample. This strategy, adequate for ionisable compounds, allows achieving an efficient sample clean-up and high enrichment factors.

CFME was developed in 2000 [9], presumably based on a previous work [7]. CFME involved the use of a glass extraction chamber, a peristaltic pump for the delivery of aqueous sample at a constant rate into the chamber (0.2–2 mL), and exposure of the solvent drop to the sample into the extraction chamber. Thus, the flowing sample solution continuously interacts with the solvent microdrop. A sample flow rate of 0.2–1.0 mL/min and an extraction time of 10–15 min used to be appropriate. In practice, the fundamental difference between DI-SDME and CFME lies in the way in which the convective-diffusive transport is favoured (magnetic agitation *vs.* sample pumping). The inconveniences of CFME were therefore similar to those of DI-SDME, which together with the requirement of unconventional equipment has meant that the contributions involving CFME have been scarce (*ca.* 20 publications).

Another three-phase SDME mode valid for the enrichment of volatiles that allows the achievement of efficient clean-up is HS-SDME, firstly introduced in 2001 [17] on the basis of the seminal works of Dasgupta and co-workers [2, 3]. Unlike other SDME modes, the physical separation of the extractant phase and sample solution occurring in HS-SDME enables its application to complex matrices. In comparison with two-phase SDME modes such as DI-SDME or CFME, HS-SDME enables the use of higher stirring rates with negligible risks of drop dislodgement and reduced sample matrix interferences. In order to extend the applicability of HS-SDME to slightly volatile and non-volatile compounds, a derivatisation strategy can be applied to form volatile derivatives that can be transferred from the aqueous sample to the headspace and trapped into the microdrop.

Inspired by a previous work where an organic drop of chloroform (1.3 μL) was placed inside a flowing aqueous drop (25–45 μL) [7], another two-phase SDME mode termed as DDSME was developed in 2006 for the extraction of target analytes present in clinical samples such as blood or saliva [10]. This SDME mode enabled a certain clean-up of the sample and transfer of the analytes to another (organic) phase compatible with the analytical instrumentation, even though the reduced sample-to-extractant phase volume ratio and the instability of the extractant phase microdrop under agitation conditions severely limited the achievable enrichment factors with reasonable extraction times. The same year, an SDME mode named as DSDME was developed [21] to overcome the limitations of previously reported two-phase SDME modes in which the syringe was used as extractant phase holder during the extraction process. DSDME is based on the use of a suspended solvent droplet in the microliter range suspended in the centre of the sample solution. However, the collection of the organic solvent after the extraction process represents the main difficulty of this SDME approach, since the solvent acquires the form of a thin layer or it is dispersed in the sample solution when stirring is stopped. Going further, a SDME mode analogous to DSDME, named as SFODME, was firstly reported in 2007 to facilitate the droplet collection after extraction [22]. SFODME requires, as in DSDME, an immiscible solvent with low volatility, low water solubility and less density than water. Additionally, solvents applicable in SFODME show melting points near room temperature (*e.g.*, 1-undecanol and 2-dodecanol). During extraction, commonly performed in a thermostatic bath, the sample vial is kept at a temperature above the melting point of the solvent. Thus, the solvent is in liquid state in SFODME

and behaves analogously to solvents used in DSDME. After extraction, the vial is cooled in an ice bath to facilitate the collection of the droplet, which solidifies, and further melts before analysis.

In 2008, inspired by both DSDME and LLLME, another three-phase SDME approach termed as DS-LLLME was introduced. In DS-LLLME, the extractant drop (usually aqueous) is suspended in the organic solvent and the latter one on the aqueous sample solution [23]. This SDME mode, however, has not attracted widespread interest.

The introduction of the different SDME modes mentioned above was followed by additional developments toward improved extractability with reduced analysis time. In this vein, the formation of an undesirable air bubble in a drop of organic solvent during microextraction processes has been repeatedly reported [24] and, a decade ago, this drawback of SDME has been demonstrated to be advantageous under controlled conditions [25]. The intentional incorporation of air bubbles into the solvent drop results in an increasing surface area, which favourably affects the extraction kinetics, as discussed in Sect. 2.2.2, and can allow obtaining higher enrichment factors. However, the reproducibility can be compromised and, additionally, large air bubbles lead to the instability of the drop. The application of vacuum for reducing the interfacial gas-phase constraints observed in HS-SDME [20] or, more recently, the use of a gas bubble flow of N_2 to favor mass transfer of volatile analytes from the sample solution to the headspace [26], have contributed to improve experimental conditions for the application of SDME approaches.

3.2 Extractant Phases in SDME

Since its first application, different extractant phases have been used in SDME comprising organic solvents, ionic liquids (ILs), deep eutectic solvents (DES), supramolecular solvents (SUPRASs), nanomaterials and aqueous drops.

Recent examples of extractant phases in SDME are included in Table 1. Different considerations should be taken into account when selecting the most suitable extractant phase, such as the nature of the sample or the target analyte/s, the microextraction modality, as well as the analytical instrumentation used. For two-phase SDME modalities, such as DI-SDME and CFME, the selected extractant phase must be immiscible with the sample and have low water solubility, high boiling point and low vapour pressure. In the case of DSDME, in addition to the aforementioned conditions, the extractant phase should have lower density than the liquid sample to be directly suspended on it. Another microextraction modality included within two-phase systems is SFODME, where the extraction solvent should have a melting point near to room temperature to facilitate its collection after solidification induced by cooling. In the case of three-phase SDME modalities, when the system is constituted by LGL phases, *i.e.*, HS-SDME, the extractant phase should have a high boiling point and low vapour pressure to minimize any evaporation during the extraction process retaining the extractant phase size and shape. Another widely used modality

is LLLME, where the critical selection relies on the intermediate liquid phase, which must be immiscible with the sample and have low solubility in water, and lower density than the sample to be adequately suspended ensuring the contact between phases. Besides, to minimize evaporation, the selected solvent should have high boiling point and low vapour pressure. Furthermore, the acceptor phase not only must be a solvent related to the target analyte according to the "like dissolves like", but this solvent should be immiscible with the intermediate phase.

As mentioned before, the selection of the most appropriate extractant phase for each SDME mode mainly depends on the physicochemical properties of the extractant phase (boiling point, vapour pressure, density, viscosity, water solubility, etc.), which will determine the formation of the drop, the extraction efficiency, as well as the compatibility with the analytical instrumentation.

Within the different type of extractant phases, organic solvents are still the most used in SDME in its different modalities (Table 1). A wide variety of organic solvents with different physicochemical properties are commercially available and ready to use without needing previous synthesis or purification procedures, offering a highly convenient option for both two-phase and three-phase systems. Moreover, considering that conventional LLE approaches usually involve the use of organic solvents, SDME makes feasible the miniaturisation of these classical methods, as long as the involved organic solvent fulfil the mentioned requirements as extractant phase, minimising the amount of solvent usage. To be selected as extractant phase, the organic solvent must fulfil a series of characteristics to avoid drop dissolution in the sample matrix or solvent evaporation during the extraction process. However, not every organic solvent meets these characteristics and can be incompatible with some analytical techniques. In addition, several organic solvents used in SDME are currently restricted or even banned by Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation in the European Union, *e.g.*, benzene, carbon tetrachloride, chloroform and toluene. In the last years, different solvent selection guides have been established with the aim of substituting those highly toxic organic solvents with less harmful ones [27–29].

ILs have been studied as greener substitutes of conventional organic solvents for extraction and preconcentration of different target analytes. ILs are organic salts constituted by an organic cation and an organic or inorganic anion that are liquid at temperatures below 100 °C. ILs offer unique physicochemical properties such as thermal stability, negligible vapour pressure, low volatility, tunable polarity and viscosity, miscibility with organic solvents and water, and structural designability. Since the first description of the use of ILs as extractants in SDME in 2003 [30], more than 65 works related to the application of ILs using the different SDME modes have been reported. Imidazolium-based ILs have been the most studied extractant phases in SDME. In addition, magnetic ILs (MILs) have emerged as improved ILs offering an inherent magnetism, which allows their manipulation using an external magnetic field, increasing the stability of the droplet during extraction [31]. Concurrently, MILs possess the typical physicochemical properties of ILs, including extremely low volatility, modulable viscosity and solubility, high ionic conductivity and high solvation properties. In the last years, different classes of MILs have been tested in

Table 1 Extractant phases in SDME techniques

SDME approach	Extractant phase	Examples of extractant phases
Two phase SDME approaches		
DI-SDME	Organic solvent	Toluene, cyclohexane, toluene/butyl acetate, toluene/hexanol, toluene/cyclohexane, octanol, decane, dichloromethane, pentanol, n-octanol, carbon tetrachloride, chloroform, amylacetate, ethanol:acetonitrile, 1-decanol, 1-undecanol, 1-dodecanol
	ILs	1-hexyl-3-methylimidazolium hexafluorophosphate
	MILs	Trihexyltetradecylphosphonium tetrachloromanganate, trihexyl(tetradecyl)phosphonium tris(hexafluoroacetylaceto)nickelate(II)
	SUPRASs	Decanoic acid and tetrahydrofuran in water, tetrabutyl ammonium hydroxide in water
	NPs-containing organic solvent	Ag-dodecanethiol NPs in toluene, Ag-citrate NPs in toluene
	DES	Hexanoic acid/thymol (1:1)
CFME	Organic solvent	Dichloromethane/ethyl acetate, carbon tetrachloride, cyclohexane
DSDME	Organic solvent	Hexane, heptane:iso-octane, toluene, xylene, 1-butanol, 1-octanol, undecanol, 2-octanone, n-butyl acetate, hexyl acetate
	SUPRASs	1-decanol in ethanol
SFODME	Organic solvent	1-undecanol, 1-dodecanol, 2-dodecacol, 1-(2-thiazolylazo)-2-naphtol, n-hexadecane; 1-chlorooctadecane, 1,10-dichlorooctadecane, 1-bromohexadecane
	SUPRASs	1-dodecanol in tetrahydrofuran; decanoic acid in water; tetrabutyl ammonium hydroxide in water
Three phase SDME approaches		
LLLME	Intermediate phase	Chloroform, dodecane, chloroform/methanol, 1-octanol
	Acceptor phase	Phosphoric acid solution, tetramethylbenzidine/hydrogen peroxide solution, sodium hydroxide solution, Au NSRs/Ag(I)
HS-SDME	Organic solvent	1-undecanol, dimethylformamide, ethyl acetate: 1,4-butanediol; toluene; n-octane; 1-butanol; methylbenzoate; n-butyl acetate; amyl acetate
	ILs	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-hexyl-3-methylimidazolium tetrafluoroborate

(continued)

Table 1 (continued)

SDME approach	Extractant phase	Examples of extractant phases
	MILs	1-octyl-3-methylimidazolium tetrachloroferrate, 1-ethyl-3-methylimidazolium tetraisothiocyanatocobaltate(II), trihexyl(tetradecyl)phosphonium tris(hexafluoroacetylaceto) manganate(II), trihexyl(tetradecyl)phosphonium tetrachloromanganate(II)
	Aqueous drop	HCl aq. solution, 5,5'-dithiobis-(2-nitrobenzoic) acid solution, Ag(I)/Fe(III)/*o*-phen/SDS in acetate buffer solution, phosphoric acid aq. solution; boric acid aq. solution, acetylacetone/ammonium acetate in acetic acid aq. solution, fluorescein/dimethylformamide aq. solution
	NPs-containing drop	Ag modified N-GQDs, Au/Ag NPs; Au/Cu NPs, Au nanoprisms/Tollen's reagent, Au NPs, CDs, Ag-citrate NCs/glutathione, Ag-PMAA NCs
	DESs	menthol:thymol (1:1), tetrabutylammonium chloride:lactic acid (1:2), choline chloride:4-chlorophenol (1:2), choline chloride:oxalic acid (1:2), tetrabutylammonium bromide:dodecanol (1:2), choline chloride:chlorophenol (1:2) - mCNTs

SDME and related microextraction techniques. The paramagnetic component of the MIL can be a metal complex (anionic or cationic) or a radical. Most applications are related to the use of MILs based on paramagnetic anions, mainly tetrachloroferrate(III) ($[FeCl_4]^-$) and tetrachloromanganate(II) ($[MnCl_4]^{2-}$) [32]. However, in spite of being considered as green solvents, it should be noted that some ILs are reported as toxic, *e.g.*, those containing fluorinated anions [32]. Furthermore, ILs synthesis usually includes a series of steps that use volatile organic solvents and thermal treatments [33]. Also, hydrophobic ILs can be adsorbed onto the sediments becoming persistent contaminants in the environment [34].

DESs are based on the combination of a hydrogen bond acceptor (HBA), such as a quaternary salt, and a hydrogen bond donor (HBD). At a certain temperature (defined as eutectic point temperature), the different components can form a homogeneous liquid phase mixture, which presents a lower freezing point than those of the individual components. DESs have similar characteristics to ILs, such as low volatility associated with low vapour pressure, chemical and thermal stability, and high tunability. The chemical formation process, along with the source of their starting materials are the main differences between DESs and ILs. DESs can be obtained by simple and low-cost synthetic procedures, which are based on heating a mixture of their individual components. Choline chloride is the most used quaternary salt due to its low cost and biodegradability. Amides, carboxylic acids, and alcohols are commonly used as HBD [35]. A disadvantage of DESs is their high

viscosity, which could lead to practical problems, including difficult handling with a micro-syringe and slow mass transfer in dissolutions resulting in longer extraction times. Besides, some DESs are not compatible with commonly used analytical techniques, such as gas or liquid chromatography, requiring dissolution in a volatile solvent or re-extraction into another solvent. Recent developments in DESs preparation are focused in developing new synthetic strategies with the aim of lowering their viscosity, making DESs more suitable for chromatographic applications. For instance, Rodinkov et al. [36] prepared a DES based on a equimolar mixture of thymol:menthol, which provides a lower viscous DES compatible for direct chromatographic analysis. The thymol:menthol DES has been applied for the extraction of toxic volatile organic compounds in atmospheric air using HS-SDME.

Surfactant-based solutions have been also used as alternative extractant phases to organic solvents in SDME. The addition of surfactants to aqueous solutions or hydro-organic media results in non-polar sites due to the generation of organised structures, like micelles, mixed micelles, vesicles or microemulsions, forming the so-called SUPRASs, also defined as nanostructured liquids immiscible with water [37]. SUPRASs are generated through self-assembly processes by dispersing a coacervating agent and an alkanoic acid in a continuous phase (water). First, surfactants coacervate three-dimensionally and then they aggregate getting immiscible with water phase. SUPRASs have unique properties, such as self-assembly synthetic procedure offering convenient and easy preparation, solvent tunability by changing hydrophobic or hydrophilic groups of the amphiphile, multi-functionality with high number of available binding sites, high surface area, low volatility, and non-flammability being a greener alternative to conventional organic solvents. The presence of distinct polarity areas in SUPRASs constituents provides good solvation capabilities for a wide range of organic and inorganic compounds. Different types of analytes are potentially extractable through different interactions, such as electrostatic and π-cation interactions, hydrogen bonds and Van der Waals forces [38].

Aqueous-based extractant phases have been also applied in SDME, mainly in three-phase systems, *i.e.*, LLL for LLLME and LGL for HS-SDME. Different aqueous solutions have been employed as acceptor phases in LLLME mode, including phosphoric acid solution, sodium hydroxide solution and colloidal liquid dispersions of nanoparticles (NPs). In the case of LGL systems, aqueous drops containing specific reagents that can selectively react with the target analyte have been reported for colorimetric and fluorescence analysis [39–41]. Furthermore, it is worth to mention that aqueous drops are easily compatible with fibre optic probes enabling fast accurate measurements for the analysis of organic and inorganic analytes. For instance, Skok et al. [39] reported an aqueous drop containing 5,50-dithiobis-(2-nitrobenzoic) acid as an optical probe combined with HS-SDME for the rapid detection of sulphite in food. Furthermore, in the last years several colloidal aqueous dispersions of nanomaterials have been employed as aqueous-based extractant phases playing the role of both acceptor phase and optical probe [42]. Analyte extraction in the aqueous drop promotes changes in the physicochemical properties of the nanomaterial, *e.g.*, fluorescence intensity, colour intensity or hue, etc., which can be used

for sensing and quantification. Most applications involve the use of noble metals NPs (Ag, Au and bimetallic Ag-Au) as colorimetric probes combined with HS-SDME. Besides, fluorescence probes based on graphene quantum dots, carbon dots and metal nanoclusters have been also reported in literature for HS-SDME mode. Also, aqueous drops can be applied as extractant phases in reversed DI-SDME for the extraction of polar analytes from water immiscible samples. Although water is considered the greenest option when selecting an extractant phase for SDME and related techniques, the use of high concentrations of other components of the aqueous-based drop, *e.g.*, acids, bases or nanomaterials, can make these methodologies less environmentally friendly in accordance with the metrics for assessing the greenness of the analytical procedure [43].

3.3 SDME Combined with Different Analytical Techniques

SDME has been combined with virtually all analytical techniques, but its combination with chromatographic techniques is particularly fruitful. In this regard, ca. 70% of original articles involve the combination of SDME with gas chromatography (GC) or liquid chromatography (LC), as discussed in Sect. 3.4. In fact, original SDME was based on the use of an organic solvent microdrop, a chromatography microsyringe and, whenever needed, in-drop derivatisation, leading to significant advantages in sample treatment prior to injection into the chromatograph. Nevertheless, the combination of SDME with spectrometric techniques such as electrothermal atomic absorption spectrometry (ETAAS), microvolume UV–Vis spectrophotometry or spectrofluorometry, and mass spectrometry (MS) has also been significantly reported.

The combination of SDME with an analytical technique is relatively easy when nature and volume of extractant phase are directly compatible with the characteristics and the sample introduction system of the concerned technique. Thus, for example, SDME is especially suitable for GC and normal phase LC if a non-polar organic solvent is employed in the drop. On the contrary, reverse-phase LC and capillary electrophoresis are more difficult to use with certain organic solvents. Although, in some cases, it is feasible to evaporate the enriched drop solvent and re-dissolve it with another suitable solvent, this procedure is not without problems. Likewise, carrying out dilution of the enriched drop eliminates some advantages of SDME. Apart from introducing additional unitary steps, a significant decrease of the achieved preconcentration factor is produced. Nowadays, conventional organic solvents, considered hazardous and polluting, are gradually being replaced in SDME by a priori less toxic solvents such as ILs or DESs. However, their compatibility with certain analytical techniques is far from ideal. For example, most of these solvents are compatible with LC but their volatility and viscosity characteristics certainly hinder their use with GC. In fact, some strategies have been developed to favour compatibility with this latter technique. In addition, as mentioned above, appropriate volumes must be introduced into the corresponding instrument. Nevertheless, different strategies have

been proposed to minimise the loss of the preconcentration achieved in the SDME procedure when the volume required for analysis is larger than the drop volume, *e.g.*, conventional nebulizers or cuvettes [44]. For example, electrothermal vaporisation (ETV) can be used for drop introduction in inductively coupled plasma-mass spectrometry (ICP-MS), thus avoiding nebulisation. Miniaturised optical instruments, accessories and optical probes allow solving the coupling of SDME with UV–vis or fluorescence detection in the drop. Other less conventional lab-made solutions will be discussed below. In general, the key to extend the use of SDME lies in being able to make measurements at the microliter level. The following is a brief description of the combination of SDME with various analytical techniques.

3.3.1 Combination of SDME with Separation Techniques

As mentioned above, separation techniques are the analytical techniques most commonly used with SDME, in particular GC. In fact, the first publications on SDME utilised GC [4], and many of SDME modes were also reported from this first time in combination with this separation technique. Probably, this can be attributed to the ideal compatibility of most organic solvents used as extractants (*e.g.*, toluene, hexane, etc.) with the separation system and the different detectors, including electron capture detector (ECD), flame ionisation detector (FID) or MS systems, which have become the most popular in combination with SDME. In addition, the coupling of SDME with capillary electrophoresis (CE) has allowed the use of CE to be extended for the determination of some bioanalyte traces and to perform chiral analysis, which would not be possible without the preconcentration and clean-up provided by a microextraction technique. In addition, SDME has the advantage of facilitating simultaneous extraction and derivatisation (in-drop or in-syringe derivatisation), which undoubtedly simplifies and shortens analysis procedures for GC, LC or CE.

Since injection in GC requires solvents with low boiling point and viscosity, solvents such as ILs or DESs are not directly compatible with the instrument. These solvents can be accumulated in the chromatograph (injection port liner and column) leading to serious problems. Notwithstanding the above, many and varied strategies have been proposed to solve this compatibility issue. Thus, for example, a removable lab-made interface has been designed for this purpose (Fig. 2). The interface allows ILs to be retained while analytes pass into the column. However, the removable unit has a reduced average life of five injections, after which it must be replaced [45]. Other strategy based on a commercially-available thermal desorption system has been proposed. Desorption of the analytes is carried out at 240 °C for 5 min [46]. The exposure of the drop into the injection port allows the volatilization of the analytes without the requirement to inject IL, thus avoiding compatibility issues [47]. Programmable temperature vaporisation (PTV) injectors have been also used for direct injection of the IL drop [48]. Although with some exceptions, GC also shows incompatibility with DESs. Dilution of the drop in an appropriate solvent

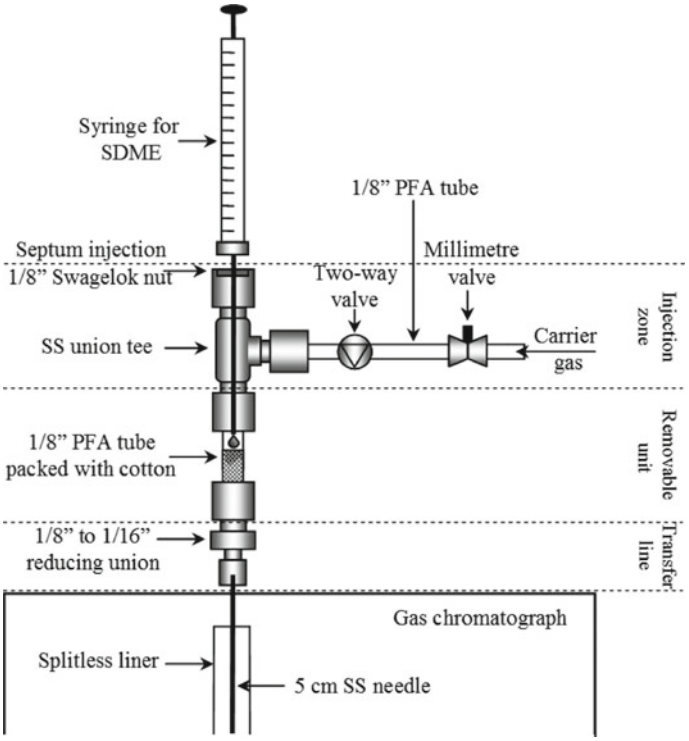

Fig. 2 Schematic diagram of the interface developed for the introduction of ionic liquids for GC–MS analysis. Reprinted from with [45] permission from the American Chemical Society

prior to the injection is generally the strategy used to protect the instrument from possible damages associated with DESs introduction [49, 50].

For combining SDME with LC, the extractant phase must be compatible with the mobile phase. Certain solvents can be directly used in the chromatograph (*e.g.*, n-hexane, o-dibutyl phthalate, cyclohexane, iso-octane, chloroform, toluene, xylene), even though the solvent is usually exchanged by evaporation and redissolution in the mobile phase [51]. However, as mentioned above, this strategy is not free of difficulties. When reversed-phase LC or CE are used for the determination of ionisable analytes, three-phase SDME approaches are often employed, taking advantage of the acid–base properties of analytes. Thus, LLLME is usual in both reverse-phase LC and CE since the enriched aqueous drop is compatible with the instrumentation. In addition, the HS-SDME mode involving aqueous drops is an important solution when volatile o semi-volatile analytes are being determined. ILs have also been used as extractants with LC and CE because they can be directly injected in the column or the capillary. For example, 1-hexyl-3-methylimidazolium hexafluorophosphate [C_6MIM][PF_6] has been injected directly for high-performance liquid chromatography (HPLC) analysis using tetrahydrofuran and methanol at pH 4 as mobile phase

[52]. In the case of CE, the capillary tip can be directly used to suspend the IL droplet [53]. Furthermore, extractants used in SFODME mode (*e.g.*, 1-undecanol) are also compatible with these techniques [54].

Automation is desirable to avoid some of the problems of SDME (*i.e.*, drop instability) while improving precision and sample throughput. In general, autosamplers and syringe pump systems (lab-in-syringe, LIS) have been used toward the automation of the SDME-GC system. In this way, partial or total automation can be achieved. A fully automated IL-based HS-SDME coupled to gas chromatography-tandem mass spectrometry (GC–MS/MS) using an autosampler was developed to determine musk fragrances in environmental water samples [55]. An automated headspace BID microextraction (automated HS-BID) has been combined with gas chromatography-mass spectrometry (GC–MS) for determining nitro musks fragrances in environmental water samples [56]. Currently, commercial versatile autosamplers enable SDME automation in a relatively simple way, even though these systems are characterised by their expensiveness. Then, lab-made autosampler robots have been reported, especially in combination with HPLC. For instance, a lab-made cartesian robot equipped with a three-way solenoid microvalve and a six-port switching valve has been proposed for the determination of triazines in coconut water samples. An Arduino Mega board was used for synchronisation of robot action, valves and analytical instrument [57]. Recently, SDME in a 96-well plate mode has been proposed as an automated format with a high-throughput analysis [58].

The combination of SDME with CE can be performed off-line, on-line and in-line. In the on-line mode, the capillary inlet tip is commonly used for hanging the drop [59]. In the in-line mode, the different steps are carried out on the CE system through automatic control. For example, in LLLME, the following stages are included: hydrodynamic injection of the aqueous extractant phase; immersion of the capillary inlet into the organic phase and drop formation; extraction of the analyte and hydrodynamic injection of the enriched drop into the capillary for analysis [60].

3.3.2 Combination of SDME with Atomic Spectrometry

The combination of SDME and atomic spectrometry has been carried out mainly with ETAAS and ETV-ICP-MS because the extractant phase volume is of the same order of magnitude as the volume required for analysis. For the same reason, other atomic techniques commonly used in analytical laboratories such as flame atomic absorption spectrometry (FAAS), atomic fluorescence spectrometry (AFS), inductively coupled plasma optical emission spectrometry (ICP-OES) or ICP-MS, which use nebulizers for sample introduction, are less suitable for microextraction purposes. Thus, the graphite furnace (GF) and ETV units are suitable for the introduction of a few microlitres, fitting well with the drop volume used in microextraction. In fact, the ETV solves the problems associated with the introduction of organic solvents into the plasma. Aqueous solutions, organic solvents and ILs have been used as extractant phases in SDME in combination with both ETAAS and ETV-ICP-MS. Aqueous solutions of Pd(II) or Au(III) have been exploited in HS-SDME to retain volatiles

generated in situ (both chemically and photochemically) from elements such as As, Se, Sb, Hg or Te [61, 62]. Hydrogen is originated as a byproduct, which leads to the reduction of noble metal ions present in the drop. The formed Pd(0) or Au(0) are able to decompose and retain the volatiles while acting as a matrix modifier in ETAAS, leading to very low limits of detection (LODs). This strategy has also been reported for simultaneous determination of As, Sb, Bi, Pb, Sn and Hg by ETV-ICP-MS [63]. When the sample is an oil, an aqueous drop can be used in the DI-SDME mode. By this way, Cd has been extracted from vegetable oil using an aqueous drop of 0.1 mol L^{-1} HNO_3 [64].

Organic solvents and ILs are commonly used in the DI-SDME mode for extracting metals in the form of complexes and ion pairs. However, certain aspects must be taken into consideration when these solvents are injected into the GF or ETV. For example, analyte losses can occur when volatile metal chlorides are formed as a result of the use of chlorine-containing organic solvents as extractant phases in SDME. In addition, extended temperature programs can be required with these solvents when compared with conventional alternatives. This is especially noteworthy in the case of ILs due to their thermal stability, high viscosity and immiscibility with aqueous solutions (*e.g.*, matrix modifiers), which can lead to difficulties in both ETAAS and ETV-ICP-MS. Dilution of the enriched IL drop with ethanol and nitric acid has been considered to reduce the viscosity of these neoteric solvents, making them compatible with the GF [65]. Other atomizers such as tungsten coils (W-coil) with a higher heating rate have also been proposed as possible solutions to these problems [66]. The combination of SFODME with ETAAS and ETV-ICP-MS has been also reported. Potential issues associated with solvent solidification in ETAAS have been minimised by means of hot injection (at *ca.* 80 °C) [67] or dilution of the enriched 1-undecanol drop with ethanol [68]. Losses of some volatile elements have been reported in ETV-ICP-MS due to the high drying temperatures required by this type of solvents. The use of mixed solvents (by addition of a solvent showing lower boiling point) has also been described. Thus, the mixture of 1-dodecanol (b.p. 259 °C) with p-xylene (b.p. 138 °C) allowed to set the drying temperature at 200 °C [69].

In general, although automated systems have been proposed, manual drop injection is still more commonly used. A certain degree of automation has been achieved with sequential injection (SI) systems. For this purpose, home-made flow-through extraction cells and commercial multiposition valves have been used [70, 71]. A fully automated HS-SDME system using a LIS system coupled with ETAAS has been proposed for Hg determination. In this case, Hg vapour is generated inside a microsyringe under reduced pressure conditions (up to 0.14 atm) without analyte losses [72].

GC can also be used after HS-SDME for sample introduction into the plasma. However, this coupling presents greater difficulties, and it is therefore less used in combination with microextraction. For example, SDME coupling with GC-ICP-MS has been used to speciation of volatile organometallic compounds [73].

As mentioned above, although the combination of FAAS with different preconcentration techniques is very popular in analytical laboratories to overcome its lack of sensitivity, FAAS has been rarely used with SDME. This is presumably attributed

to the higher volumes required by the nebulisation system compared to those used in SDME. For this reason, the drop is usually diluted prior to measurement. For example, SFODME has been employed in combination with a FI-FAAS system for Cu(II) determination in water by using a 1,5-diphenylcarbazide-containing 1-undecanol microdrop as extractant. Dilution of the solidified drop to 300 μL with ethanol was required for this purpose [74]. Speciation of Cr(III) and Cr(VI) using DSDME required a home-made micro-sample introduction system and dilution of the extraction solvent (1-octanol) with an ethanol/0.1% (v/v) HNO_3 solution [75].

Likewise, AFS has been used after SDME with dilution and/or acid treatment of the drop, so that the typical advantages of SDME are not fully exploited. For example, HS-SDME using IL as extractant phase has been combined with AFS for the determination of organomercurials. In this case, the enriched drop was mixed with an acidic potassium permanganate solution to oxidise organomercurial species to inorganic mercury [76]. In addition, a method based on the combination of SFODME with hydride generation (HG)-AFS for Se(IV) determination has been reported, involving complex formation with ammonium pyrrolidinedithiocarbamate (APDC) and its extraction by a microvolume of 1-undecanol. Back-extraction was then performed using 300 μL of a 5 M HNO_3 solution for HG-AFS analysis [77]. 1-undecanol has also been used as extractant phase in SFODME for determining Hg by cold vapour (CV)-AFS. The method involved the extraction of a hydrophobic complex of the metallic ion (mercury diethyldithiocarbamate) followed by the dilution of the enriched drop with 2 mL of ethanol for analysis [78].

X-ray fluorescence-based techniques are a priori compatible with SDME because only a few microlitres are required for measurement. In fact, DI-SDME has been combined with energy dispersive X-ray fluorescence spectrometry (EDXRF) [79] and total reflection X-ray fluorescence (TXRF) [80] as a strategy to improve the LODs. However, the deposition of the enriched extractant phase for analysis represents the main problem to be addressed with these techniques. Particularly, it is necessary to avoid spillage on the sample carrier surface, for which different alternatives have been proposed. In the case of EDXRF, this issue has been solved by applying consecutive deposition/drying of the organic phase in small portions on a Whatman filter. Regarding TXRF, it required solvent exchange by replacing benzene by a significantly more polar solvent, specifically an aqueous solution containing an internal standard [80]. In this case, the enriched aqueous solvent was deposited on the sample carrier made of quartz, which was previously coated with a hydrophobised silicone solution.

Laser-Induced Breakdown Spectroscopy (LIBS) has also been proposed for measurement after SDME in spite of the problems shown by the technique when dealing with liquid phases. Two possible strategies have been evaluated. On the one hand, the analysis of the droplet suspended in the syringe tip. On the other hand, the analysis of the dried droplet on a substrate (surface-enhanced LIBS technique, SENLIBS). While the first option was found to be not suitable for analytical purposes due to lack of sensitivity and precision, SENLIBS was considered a promising alternative in combination with microextraction [81]. SDME with a toluene drop has been

used for extraction of Cr, Mn, Ni, Cu and Zn APDC chelates followed SENLIBS measurement after drying the drop on an aluminium substrate [82].

3.3.3 Combination of SDME with UV–Visible and Fluorescence Spectrometry

As already noted, the incompatibility of the drop volume with conventional UV–vis spectrophotometry or fluorospectrometry has led to a later development of the combination of these techniques with SDME. In fact, drop dilution and/or use of microvolume cuvettes are still considered as a solution even though it implies a loss of sensitivity. Notwithstanding the above, special optical systems such as liquid droplets, liquid films/droplets and falling drops were initially proposed in combination with SDME without requiring dilution [83]. In general, the miniaturisation of sample compartment, radiation sources and detectors have been key to achieve SDME-compatible systems. At present, microvolume spectrophotometers and spectrofluorimeters, optical probes and smartphones are available for this purpose, greatly facilitating the combination of SDME with molecular spectroscopy.

Commercial confined drop-based UV–vis spectrometers and fluorospectrometers greatly facilitate the measurement of the enriched extractant phases from SDME. These systems are equipped with a system for depositing the drop between two pedestals to form a measurement column within the optical path. The characteristics of the extractant phase must be compatible with this system in order to form the column, while avoiding chemical attack of the pedestals and minimise losses by evaporation during measurement. In addition to aqueous solutions, many organic solvents (e.g., N,N'dimethylformamide, toluene, xylene, methyl isobutyl ketone), ILs and DESs can be used for measurement with these instruments [83]. In general, these systems have a lower path length in comparison with conventional spectrophotometers, which is undoubtedly a drawback when it comes to take advantage of the full potential of SDME. However, it may be compensated by the high preconcentration factors that can be reached in some cases. A large number of applications have been proposed involving SDME approaches involving both miniaturised UV–vis spectrometry and fluorospectrometry. In-drop derivatisation with conventional reagents for forming coloured or fluorescent compounds were initially purposed. Some examples include the colorimetric determination of nitrite by HS-SDME using a Griess reagent-containing aqueous drop for simultaneous extraction and derivatisation [84] or the fluorimetric determination of formaldehyde in textile samples using in-drop Hantzsch reaction [85]. The fluorescence enhancement or quenching of the droplet has also been exploited for sensing, *e.g.*, for determining bromide after in situ generation of volatile bromine and its trapping by a fluorescein-containing aqueous drop [41]. Within the different extractant phases, those containing nanoparticulated materials have greatly extended the use of these couplings. Thus, for example, the fluorescence quenching of quantum dots (QDs) when exposed to H_2Se was used for Se(IV) determination [86]. Remarkably, NPs have made it possible extending the application of SDME to the amplification of signals of DNA and microRNA analysis [87]. A

confined drop-based UV–vis spectrometer has also been used for turbidity measurement after HS-SDME and precipitation of the analyte in the drop [88]. This strategy eliminates typical interferences in turbidimetry, such as absorbance, turbidity and/or fluorescence from the matrix and scattering and background fluorescence associated with optical windows.

Although to a lesser extent, optical systems that avoid the necessity of transferring the drop to the measurement instrument have also been used with SDME. Thus, an optical probe was proposed as both microdrop holder and measurement cell, then enabling the continuous monitoring of the extraction. As a proof of concept, sulphites were determined in this work by using the optical probe to expose an aqueous microdrop containing Fe(III) and 1,10-phenanthroline (adjusted at pH 5.6) to the headspace above the sample. In particular, volatile SO_2 reduces Fe(III) to Fe(II) in the drop, leading to the formation of a red coloured complex with 1,10-phenanthroline [89]. Optical probes can be also used with DI-SDME and LLLME modes [90]. A micro-pipette system was designed for integrating different unitary steps, fulfilling the functions of extractant handler, microdroplet holder and microcuvette for in situ absorbance measurement [40]. LIS automation in combination with miniaturised fibre optic systems is another interesting option that allows to eliminate drop transfer for analysis (Fig. 3) [91, 92].

The camera of mobile phones is nowadays an analytical detector of great interest and has also been used in combination with SDME in order to capture images of the drop. In this sense, the low sensitivity and selectivity reached by the camera can be solved by the preconcentration and clean up capacity of the microextraction strategy. Thus, for example, HS-SDME combined with mobile phone has been used for formaldehyde determination using a box illuminated by a white LED to obtain reproducible digitisation conditions [93]. In addition, pH-induced aggregation of

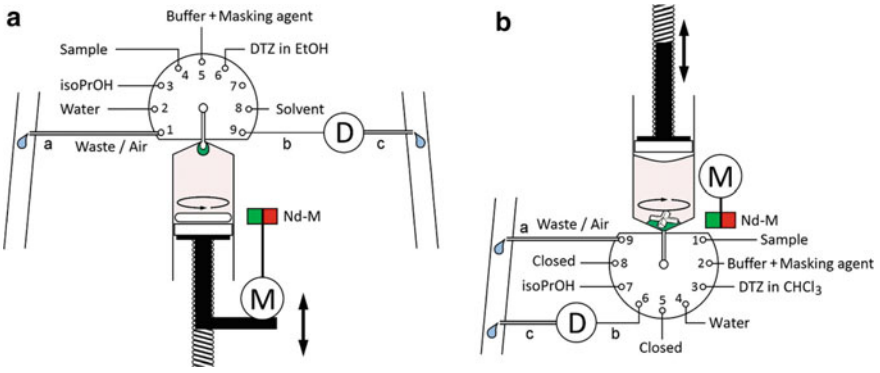

Fig. 3 **a** Schematic diagram of the DI-SDME into a floating drop **b** Schematic diagram of the in-drop stirring assisted DI-SDME (tubing dimensions of a: 5 cm, 0.8 mm i.d., b: 5 cm, 0.5 mm i.d., c: 5 cm, 0.5 mm i.d., all made from PEEK capillary. DTZ: dithizone, isoPrOH: isopropanol, M: DC motor, Nd-M neodymium magnets). Reprinted with permission from Elsevier [92]

biomass carbon dots (CDs) has been exploited for ammonia detection using a smartphone with colorimetric and fluorescent readout after HS-SDME [94]. This combination has also been recently used for determining hydrogen sulphide in biosamples with silver−gold core−shell nanoprisms (Ag@Au np) through the inhibition of absorbance of the Ag@Au np induced by the analyte [95].

3.3.4 Combination of SDME with Mass Spectrometry

Direct coupling of SDME with MS has also been reported. This coupling has allowed the applications of SDME to be extended to the determination of biomolecules, including proteins, peptides, carbohydrates, lipids, metabolites, bacteria, etc., in complex matrices. Matrix-assisted laser desorption/ionization (MALDI)-MS is generally used for this purpose. The volume required for measurement by MALDI-MS fits well with that used in SDME. Furthermore, the drop can be deposited directly on the target plate preventing further drop manipulation.

The extractant used in SDME must be miscible with the MALDI matrix solution, have a certain volatility and ensure the formation of homogeneous crystals with the matrix. In addition to conventional organic solvents such as octanol, toluene, chloroform, octane, etc., ILs have also been used as extractants, in many cases in combination with NPs. For instance, a toluene drop containing gold or silver NPs and tetraalkylammonium bromide has been proposed for DI-SDME of peptides. The isoelectric point of the peptides and the surface charge of the gold NPs were key to achieving the separation [96, 97]. A drop of IL (1-butyl-3-methylimidazolium hexafluorophosphate) containing platinum NPs was used for extraction of Gram-negative bacteria and subsequent detection using a time-of-flight (TOF) detector (MALDI-TOF-MS). In this case, the positively-charged head group of IL attracts membrane proteins of bacteria [98]. In general, NPs, in special silver NPs, have received a high degree of interest for ionisation and preconcentration in MS combined with SDME [99].

The combination of DI-SDME with paper spray mass spectrometry (PS-MS) has been recently proposed as an improved strategy [100]. In this case, the drop is added onto the tip of a paper triangle and a high voltage is applied to generate the ionisation.

Automation is also desirable in the coupling SDME-MS. In this sense, droplet-in-droplet and droplet-on-droplet microfluidic microextraction systems have recently been developed using a liquid-handling robot to work in the nanolitre-scale [101].

3.3.5 Combination of SDME with Electrochemical Detection Techniques

Electrochemical detection has been rarely used with SDME in spite of its interest in eliminating matrix interferences. This is probably due to the fact that solvents used in the drop are not always compatible with this type of detection. In this sense, the combination of SDME with potentiometric detection has been proposed for the

determination of caffeine in saliva by means of a SI system. It was carried out by solvent change (evaporation and redissolution in an aqueous phase). As mentioned above, this strategy leads to the loss of the preconcentration factors achieved with SDME [102]. Voltammetric detection has also been used for the determination of ascorbic acid after SDME using a magnetic IL dissolved in ethanol as extractant phase. After recovery of the IL by a magnet, it was diluted in ethanol and transferred onto the surface of a carbon paste electrode (CPE) modified with TiO_2 NPs [103]. Conductimetry has also been used with HS-SDME integrated in a lab-made automatic flow-batch system for ammonium determination. This mode of SDME eliminates the solvent problem [104].

3.3.6 Combination of SDME with Other Techniques

Infrared (IR) spectroscopy has been used in a simple way after SDME. In general, the extraction of hydrophobic complexes of analytes by an organic drop eliminates two major problems of IR spectroscopy, namely poor sensitivity and interference from water. After extraction, the drop is directly deposited on the corresponding substrate and dried for the measurement. Thus, for example, Cr(VI) [105] and vanadate [106] complexes with hydroxy-N1,N2-diphenylbenzamidine have been extracted in a dichloromethane drop, whereas a dichloroethane drop has been used for extraction of a Mo(VI) complex with N1-hydroxy-N1,N2-diphenylbenzamidine [107]. Diffuse reflectance Fourier transform infrared spectroscopy (DRS-FTIR) has been used in these cases after SDME. To this end, the enriched drop was deposited over the KBr substrate and dried before filling the sample holder. Furthermore, perchlorate has been extracted as ion-pair with cetyltrimethylammonium in methyl isobutyl ketone. In this case, the drop is directly placed and dried on the zinc selenide crystal substrate of the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectrometer for analysis [108]. Recently, modified silver NPs have been implemented in the drop to enhance the signal intensity for tartrazine [109] and quaternary ammonium cationic surfactants [110].

Ion-mobility spectrometry (IMS) is a low-cost and fast analytical technique that is usually used after extraction methods to increase selectivity. In this regard, IMS has been combined with SDME [111–113]. The main drawbacks of this coupling come from the injection of organic solvents in the IMS system, which lead to high blanks. To solve these problems, IMS has been combined with IL-based HS-SDME with room temperature gas chromatography (RTGC) for on-site IMS analysis [111]. The design of a special injection unit for the retention of the IL in a glass wool before it reaches the IMS unit was necessary for this purpose [112]. More recently, LLLME has been proposed for the determination of psychotropic drugs in urine using IMS with electrospray ionisation (ESI). This coupling solves the problem caused by the need to mix the aqueous solution with methanol or acetonitrile to increase the ionisation efficiency in ESI [114].

Chemiluminescence has been also used in combination with SDME. Thus, for example, LLLME has been used for Sb(III) and total Sb determination through

the inhibition of the chemiluminescence from the CdSe QDs/H_2O_2 system in the presence of antimony species using a tube luminometer for measurement [115].

Moreover, SDME has recently been combined with surface-enhanced Raman scattering (SERS) to increase the sensitivity of the technique. For instance, a drop of toluene was used as extractant phase for the preconcentration of p-mercaptobenzoic acid (p-MBA) using DI-SDME. After microextraction, repeated cycles of deposition/drying of the droplet onto the SERS substrate (*i.e.*, gold nanohole array substrate) were carried out. A sensitivity improvement of three orders of magnitude with a relative standard deviation (RSD) of 21% was achieved under these conditions. However, the procedure has not yet been proved to be suitable for application in real samples [116].

In addition, a procedure of HS-SDME using a gold NPs-containing aqueous drop has been proposed for the determination of captopril by a microchip coupled with photothermal lens microscopy (PTLM). This technique uses coaxial excitation and probe lasers focused onto the sample under an optical microscopy. This results in a local heating that produces a concave lens effect which responds to analyte concentration and thermo-optical properties of the medium. In the procedure proposed by Abbasi-Ahsd et al., the interaction of the thiol groups of captopril with the AuNPs present in the drop result in the reduction of the PTLM signal of AuNPs, leading to significantly increased linearity and sensitivity [117].

MILs-based SDME has been used for DNA extraction to direct quantitative polymerase chain reaction (qPCR) amplification, reaching high enrichment factors with an extraction time of 2 min [118]. This combination solves some of the reported problems related to the conventional methods used in DNA purification, such as the use of reagents that can inhibit qPCR in traditional methods or the low extraction efficiencies values achieved when magnetics beads are employed.

4 Performance Overview and Recent Applications

The overall performance of SDME approaches and recent selected applications are discussed in this section.

Figure 4a shows the evolution of the publications related to SDME from its first developments in the mid-1990s. The contributions involving SDME sharply increased since 2003 and peaked in 2009. Thereafter, the number of works gradually decreased and, since 2014, the scientific output involving SDME has remained almost constant at an average of 25 publications per year. In total, more than 700 articles have been published related to SDME. Figure 4b shows the annual evolution of publications involving each of the SDME techniques. Additionally, the pie chart (Fig. 4b) provides information on the proportion of the different SDME modes during this period (1995–2022). HS-SDME and DI-SDME are used in almost two thirds of the total, with similar figures, higher for HS-SDME than for DI-SDME, followed by other modes such as CFME, LLLME, DDSME, DSDME and SFODME. Regarding the evolution of each SDME mode per year, DI-SDME became the most popular SDME

mode from 1995 to 2010, whereas HS-SDME was the most widely used approach during the period 2011–2022. The decline in the frequency of publication of DI-SDME contributions can be attributed to the increasing popularity of other two-phase microextraction techniques such as DLLME. Additionally, SFODME received more attention than other SDME modes previously developed such as CFME, LLLME, DSDME and DSDME in the period 2011–2022.

Ring graphs were also designed to show a general perspective of the type of analytes determined (Fig. 4c), the analytical technique coupled to SDME (Fig. 4d) and the type of samples analysed (Fig. 4e). As shown in Fig. 4c, organic compounds were the most evaluated analytes (71%), even though metals, organometallic

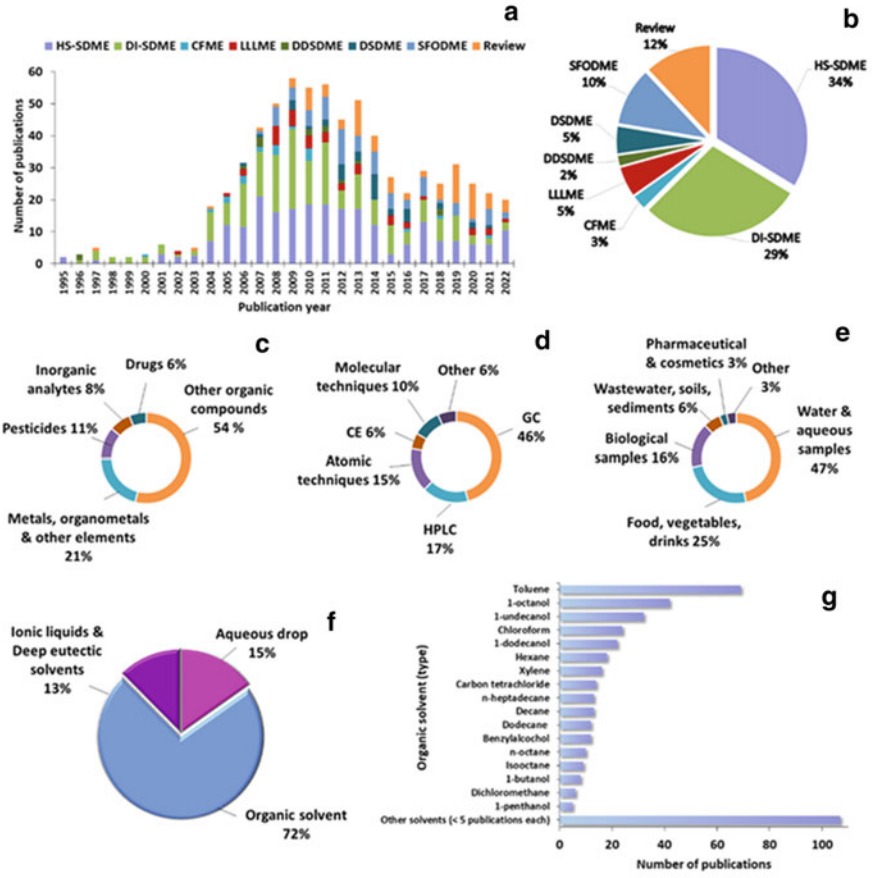

Fig. 4 Information of the publications related to SDME. **a** Vertical bar chart of the number of publications per year devoted to SDME. **b** Pie chart of the SDME modalities. **c** Ring graph related to the type of analyte. **d** Ring graph devoted to the techniques coupled to SDME. **e** Ring graph focused to the type of sample. **f** Pie chart of the type of drop. **g** Horizontal bar chart of the organic solvents most used

compounds and inorganic anions were also determined. As shown in Fig. 4d, the analytical techniques more commonly associated with SDME were separation techniques (69%). GC is used in most of contributions (43%) coupled to different detectors, including, in order of usage, MS, FID and ECD detectors. HPLC and CE have also been significantly used (17% and 6%, respectively). For contributions involving HPLC, the UV–vis detector was most commonly applied. The most used atomic techniques for the determination of metals were ETAAS and ETV-ICP-MS.

In relation with the type of samples analysed (Fig. 4e), aqueous samples (*e.g.*, river, tap, well, lake, drinking waters) were the most studied samples (47%), probably due to the low concentration levels of target analytes, which requires high enrichment factors to carry out the determination, apart from the relatively simple matrix of these samples. Nevertheless, more complex samples such as foods, drinks, biological samples (*e.g.*, blood, urine, saliva, hair) and environmental samples, such as soils or sediments, have been analysed.

As discussed in Sect. 3.2, extractant phases of different nature have been used in SDME, including organic solvents, aqueous drops, ILs and DESs. Organic solvents are by far the mostly used extractant phases, being used in more than 70% of the total number of publications (Fig. 4f). Notwithstanding this, aqueous microdrops containing metal ions, metallic nanomaterials, and surfactants have been significantly employed (15%) with a frequency similar to that of ILs and DESs (13%). Aqueous microdrops were mainly applied with three-phase SDME approaches, including both LLLME and HS-SDME.

Finally, the most used organic solvents in SDME can be seen in Fig. 4g. Specifically, toluene, 1-octanol, 1-undecanol, chloroform and 1-dodecanol were the five most commonly used organic solvents. It is worth mentioning that solvent selection depended to a high extent on the SDME mode used. For instance, toluene was used in DI-SDME, DDSDME, DSDME, HS-SDME, LLLME; 1-octanol was employed by HS-SDME, DSDME, DI-SDME, DDSME and 1-undecanol was mainly used in SFODME.

As it can be seen, SDME has been applied to a wide range of samples and analytes using different modalities/approaches (mainly DI, HS, LLLME, BID).

However, it could also be interesting to focus on the most recent applications to envisage future advances. In Table 2, selected applications have been included as an example of the most recent publications. Information related to the drop composition, LOD, EF, precision and the analytical technique were included for the different applications. As we can see, in the last five years, diverse drop types were applied, such as organic solvents, ILs, DESs, MILs, NADES, noble metals and NPs. Furthermore, SDME was coupled to almost all types of analytical techniques. High EF, up to 1600, were achieved for certain publications related, for instance with pesticides. Precision evaluated as RSD(%) was lower than 10% for most applications.

Applications to a huge variety of analytes have been carried out over the last years, including pesticides, alcohols, PAHs, parabens, terpenes, heavy metals, ammonium, hydrogen sulphide, DNA, etc. While most applications have been carried out using

Table 2 Selected applications of SDME for the determination of organic compounds, metal species, anions and biomolecules published in the last five years

SDME approach	Analyte	Solvent/Drop composition	Sample	Analytical technique	LOD	EF	Precision (RSD, %)	Ref.
SDME	Ranitidine	CH_2Cl_2	Waters	LC–MS/MS	9.4×10^{-9} mol/L	45	4.3	[119]
DI-SDME	Cu(II)	Decane	Tap water	GF-AAS	0.025 μg/L	45.2	6.8	[120]
BID	Carbamate pesticides	Toluene and butyl acetate	Waters	GC–MS	0.02–0.04 μg/L	536–1097	7	[121]
HS-SDME	Triazole pesticides	DESs	Fruit juice, vegetables	GC-FID	0.82–1 μg/L	273–346	3.9–6.2	[122]
HS-SDME-SP	As(III), As(V)	Ag(I) + Fe(III) + o-phen + SDS	Waters	UV–vis Spectrometry	0.1×10^{-9} mol/L	–	2	[40]
HS-SDME	Phenols, aliphatic alcohols	DES	Air, gas mixtures	GC-FID	0.001–0.01 mg/L	–	5	[36]
HS-SDME (gas-flow assisted)	BTEXs	1-undecanol	Waters	GC-FID	0.52–0.63 μg/L	–	3.2–5.1	[26]
HS-SDME	PAHs	DES	Waters	GC–MS	0.003–0.012 μg/L	–	3.9–7.2	[50]
Pa-SDME	Several organics	MIL	Waters	HPLC–DAD	1.5–3 μg/L	10–14	1–21	[58]
HS-SDME	Formaldehyde	N-GQDs-Ag	Milk	Luminescence	1.7×10^{-4}% w/v	–	0.7	[123]
LLLME-SDME	HTL	Several	Human urine	CZE	$25 \times 10–^{9}$ mol/L	340	4	[124]
DI-SDME	Vanadium	$[C_6MIM][PF_6]$	Water	Digital colorimetry	0.6 μg/L	50	4.8	[125]
HS-SDME	Methanesulphonates	$[BMIM]TF_2N$	APIs	HPLC–UV	15 ng/mL	–	1–2.8	[126]
DI-SDME	NSAIDs	3-phase	Human urine	In-line CE-UV	2–10 ng/mL	960–1610	0.6–1	[127]
HS-SDME	Organic pollutants	SUPRADESs	Waters	HPLC–UV	0.1–14.6 μg/L	2.1–961.1	2.3–9.9	[128]
HS-SDME	Methanol	DMF	Wine	GC-FID	1 μg/L	–	1.9–4.8	[129]

(continued)

Table 2 (continued)

SDME approach	Analyte	Solvent/Drop composition	Sample	Analytical technique	LOD	EF	Precision (RSD, %)	Ref.
DI-SDME	Acrylamide	n-octanol	Food samples	GC-ECD	0.6 μg/L	–	<6	[130]
HS-SDME	Formaldehyde	Au-np/TR	Food samples	Smartphone and UV–vis Spectr	30×10^{-9} mol/L	–	<4.6	[131]
HS-SDME	Ammonium	Boric acid	Waters	On-drop conductometry	2.8 μM		3	[104]
DI-SDME (Lab-in-syringe)	fluoroquinolones	NADES	Waters	HPLC-fluorescence	6–9 ng/L	35–45	0.2–5.9	[132]
HS-SDME	2-phenoxyethanol	Octane	Fish	GC–MS	0.2 μg/mL		<5	[133]
HS-SDME	ammonium	phosphoric acid	Water and food	UV–vis microspect	0.14 mg/kg	38–137	4.8–6.3	[134]
HS-SDME	Ethyl carbamate	Ethyl acetate	Wine	GC–MS	1.5 ng/mL	–	2.2–4.8	[135]
HS-SDME	CdTe QDs Te(IV)	$AuCl_4^-$	Waters	GF-AAS	0.13 μg/L Te(IV) 0.03 Total Te	14–101	<4.2	[62]
MTME-SD	Chloramphenicol	NTs/G-quadruplex/ PPIX	Milk, urine	Fluorescence	0.00856 fg/mL	–	<5.5	[136]
HS-SDME	NH_3, pH	CDs	Water	Smartphone	34 μM	–	–	[94]
HS-SDME	Methanol, ethanol	DMSO	Industrials oils	GC-FID	0.02 (m), 0.03 (e) μg/g	–	1.8–5.2	[137]
MTP-SDME	DNA, microRNA	Three-phase	Serum samples	UV–vis microspectr	0.15–0.34 aM	27	<5	[87]
HS-SDME	H_2S	Ag@Au-np	Egg, milk	Smartphone	65 nM	–	<4.8	[95]
HS-SDME (WCS)	H_2S, I_2, Br_2, Hg	Au@AgNPs and AuNRs	Waters	Smartphone	0.46 μM H_2S	–	4.4	[138]
SDME	Tartrazine	Toluene with AgNPs	Foodstuffs	DRS-FTIR	2.44 ng/mL	–	1.76	[109]

(continued)

Table 2 (continued)

SDME approach	Analyte	Solvent/Drop composition	Sample	Analytical technique	LOD	EF	Precision (RSD, %)	Ref.
Dynamic-SDME	Parabens	dichloromethane	Waters	HPLC–UV UHPLC-MS/MS	0.3 μg/L	–	5.54–17.94	[139]
On-line SDME	Amide herbicides	CCl_4	Rice samples	GC–MS	0.3–1.5 μg/kg	–	1.9	[140]
Pa-SDME	Pesticides	MIL	Human urine	HPLC–DAD	7.5 μg/L	4–15	3–17	[141]
SDME	muscimol, psilocin	Octanol	Urine	CE	0.004 mg/L (muscimol) 0.016 mg/L (PSC)	170	0.3–8.5	[142]
Three-phase SDME	HTL	$CHCl_3$	Urine	CE	0.04 μM		6.4–10.2	[143]
HS-SDME	Se(IV)	AuNPs	Seawater, tap water	Digital colorimetry	12 μg/L (LOQ)	–	4–5	[144]
HS-SDME	Terpenes	DESs	Spices	GC–MS	0.47–86.4 μg/g (LOQs)		<20	[145]
DI-SDME and CFME	Mn(II)	PAN/$[C_4MIM][PF_6]$	Tonic drinks, seafood	GF-AAS	3.9 and 7.9 ng/L	18 and 15	6.2 and 6.9	[146]
DI-SDME	PBDEs	Chlorobenzene	Waters	GC–MS/MS	6 ng/L	8–60	7.5–25	[147]
DI-SDME	p-MBA	Toluene	Water	SERS	10^{-8} mol/L	1000	21	[116]
SDILNDμE	As, Cd, Ni, Pb	$[C_4MIM]$ $[PF_6]$ IL	Eye makeup products	ETAAS	0.049–0.262 μg/L	48–57	<4.2	[65]
SDME-LVSEP	Herbicides	Pentanol	Soil	CE-MS	2–4 nM	600–1300	10–11	[148]
CCU-CF-SDME	PAHs	Cyclohexane	Waters	GC–MS	0.0012–0.0101 μg/L		0.5–6.4	[149]
HS-SDME	Hg(II)	AuNPs	Waters	Colorimetry	1 nM	–	–	[150]

(continued)

Table 2 (continued)

SDME approach	Analyte	Solvent/Drop composition	Sample	Analytical technique	LOD	EF	Precision (RSD, %)	Ref.
DI-SDME (LIS) (two modes)	Pb(II)	Dithizone	Water	UV–vis spectr	23–75 nmol/L	18	4.2–4.8	[92]
LLLME	Patulin	Ethyl acetate	Apple juice	LC–MS/MS	0.5 μg/L	–	3.6	[151]
HS-SDME	Total Br	AuNPs	E-waste polymers	UV–vis spectr	8.8 ng/mL	–	4.8	[152]
HS-SDME	formaldehyde	Acetylacetone	Textile, wastewater	Smartphone	0.1 mg/L	–	2.7–5.1	[93]
SDME	Sb(III)	BPHA-[C_4MIM][PF_6]	Water	GF-AAS	0.01 μg/L	112	4.2	[153]
HS-SDME	BTEX	DESs (MBGs)	Water, urine	GC-FID	0.05–0.9 ng/mL	520–587	<10%	[49]
SDME	Perchlorate	Ion-pair	Soil, water, milk, urine	ATR-FTIR	0.003 ng/mL	–	1.9–2.7	[108]
HS-SDME	Chlorobenzenes	MIL	Waters	GC–MS	4–8 ng/L	–	3–18	[154]
HS-SDME	Thiomersal	AuNRs	Pharmaceuticals	UV–vis spectr	0.5 ng/mL (Hg)	–	8.4	[155]

chromatographic separations coupled to mass spectrometry (e.g. LC–MS/MS, GC–MS), other detectors such as DAD, FID, UV have also been reported. Some spectrometric techniques such as ETAAS, SERS, UV–vis spectrophotometry, FTIR as well as digital colorimetry have also been applied.

5 Conclusions and Future Trends

SDME has established itself as one of the most powerful LPME techniques for analyte enrichment and sample clean-up. However, this technique has faced from the early developments, several drawbacks that have limited its use such as risk of drop detachment when supported on the tip of syringes, limited drop volume, extractant solvent volatility and impaired precision. New progress in this technique has occurred so as to alleviate these shortcomings such as some attempts to automate extraction procedures, implementation of novel extractants with enhanced preconcentration ability, better thermal stability, high viscosity, low volatility and adjustable miscibility as well as new extraction modes. Apart from conventional organic solvents used as extractant phases in first developments, others phases with more appealing properties such as ILs, DESs, SUPRASs, nanomaterials, etc. have emerged in the last years. Advances in the combination of SDME with a broad variety of detection techniques should also be highlighted. In order to increase sample throughput and improve precision, several automated procedures have been reported in the literature using lab-made autosamplers, lab-in-syringe platforms and well plate systems. Undoubtedly, robotics is called to play an important role in the advances to be expected in next years concerning SDME automation. Apart from the above properties, green chemistry guidelines should also be taken into account for the selection of non-toxic and environmentally-friendly extractants.

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