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Review

Critical overview of selected contemporary sample preparation techniques

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ABSTRACT

Sample preparation procedures in use in many application areas are still tedious and manually intensive protocols. These characteristics mean that sample treatment is considered the most time-consuming and error-prone part of the analytical scheme. The increasing demand for faster, more cost-effective and environmental friendly analytical methods is a major incentive to improve these conventional procedures and has spurred research in this field during the last decades. This review provides an overview of the most relevant developments and successful approaches proposed in recent years concerning sample preparation. The current state-of-the-art is discussed on the basis of examples selected from representative application areas and involving conventional instrumental techniques for the final determination of the target compounds. Emphasis will be on those techniques and approaches that have already demonstrated their practicality by the analysis of real-life samples, and in particular on those dealing with the determination of minor organic components. The potential of the latest developments in this field for sample treatment simplification and complete hyphenation and integration of analytical process is discussed and the most pressing remaining limitations evaluated.

Contents

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Abbreviations: DDME, drop-to-drop micro-extraction; DLLME, dispersive liquid–liquid micro-extraction; DPX, disposable pipette extraction; d-SPE, dispersive solid-phase extraction; DUSE, dynamic ultrasound-assisted extraction; EME, electromembrane extraction; FMAE, focused microwave-assisted extraction; HF(2/3)ME, hollow fiber-protected two-/three-phase micro-extraction; HS, headspace; ISPE, immuno solid-phase extraction; LLE, liquid–liquid extraction; LLLME, liquid–liquid–liquid micro-extraction; LVI, large volume injection; MAE, microwave-assisted extraction; MASE, membrane-assisted solvent extraction; MEPS, micro-extraction in packed syringe; MIP, molecular imprinted polymer; MSPD, matrix solid-phase dispersion; PMAE, pressurised microwave-assisted extraction; PLE, pressurised liquid extraction; SBE, solvent bar micro-extraction; SBSE, stir-bar-sorptive extraction; SDME, single-drop micro-extraction; SFE, supercritical fluid extraction; SLE, solid–liquid extraction; SME, solvent micro-extraction; SPE, solid-phase extraction; SPME, solid-phase micro-extraction; SSC, single short column; SWE, subcritical water extraction; UA-MSPD, ultrasonic-assisted matrix solid-phase dispersion; USE, ultrasound-assisted extraction.

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1. Introduction

Analytical procedures typically consist of a number of equally important steps for sampling, sample treatment, isolation of the target compounds, identification, quantification and data handling. All operations and manipulations carried out with samples before instrumental determination of the tested compounds are considered to be part of the sample treatment/preparation step. Sample preparation would consequently include from labelling and mechanical processing and homogenisation of the studied matrix, to any type of gravimetric or volumetric determination carried out to characterise the analysed (sub-)sample, as well as all subsequent treatments designed to decompose the matrix structure, to perform the fractionation, isolation and enrichment of the target analytes from any potential interference, to make the tested compound(s) compatible with the detector (e.g., phase exchange and derivatization reactions), and to improve their detectability. Nevertheless, the term *sample preparation* has typically been associated to the latter group of chemical operations, all earlier mechanical and basic treatments being named as *sample pre-treatment* [1]. This will also be the terminology applied in the present review article.

Considering the nature and goal of most sample preparation operations, it is evident that this part of the analytical process has a profound influence on both the total time required to complete the analysis and the quality of the results obtained. However, it has only been in recent years that this step has risen to the prominent place that it now holds within the analytical protocol. The development of trace-level determinations in environmental and food samples have been identified as generating the stimulus for much of the progress in this research area [2]. Whatever the original incentive, it is clear that the continuous demand for accurate and faster determinations of a constantly increasing number of analytes at decreasing concentrations in these complex matrices, together with the increasing interest for the analysis of biological samples and the development of the –omics sciences, have spurred investigations in this active research field.

Despite the many efforts carried out during the last two to three decades to improve the techniques used for sample preparation, the sample treatment procedures in use in many application areas are still tedious multistep protocols involving repeated manual manipulation of the extracts. Because of the frequently low concentrations at which the target analytes should be determined, the first step of these protocols usually consists of the exhaustive extraction of the analytes from the matrix in which they are entrapped. The essentially non-selective nature of this initial step makes subsequent purification of the obtained extracts before final instrumental determination mandatory, unless (separation-plus)-detection is highly selective. The several analytical treatments involved in these purification protocols are usually carried out off-line, which significantly affects throughput and analysis cost both in terms of time and reagent consumption, makes the procedures prone to contamination and degradation of the analytes, and often results in the generation of relatively large amounts of waste. These features explain why sample preparation is estimated to accounts for two-thirds of the total analysis time and, more importantly, is considered to be the primary source of errors and discrepancies between laboratories [3]. In other words, proper selection and optimisation of the sample preparation scheme are key aspects within the analytical process that can greatly affect the reliability and accuracy of the final results [4,5].

Conventional techniques, such as liquid–liquid extraction (LLE), solid–liquid extraction (SLE) and Soxhlet extraction, are still widely accepted and used for routine applications and/or for reference purposes. However, in recent years, some of these techniques have been revisited and upgraded versions, in which their most pressing shortcomings have been solved, are now available. The studies in this field have also led to the development of new faster and more powerful and/or versatile extraction and preconcentration techniques [6]. Thereby, in many instance, partial and even full hyphenation and automation of the analytical process, or at least of the several treatment steps, are now possible. In addition, sample preparation approaches that fulfil the goals of green analytical chemistry [7] are also available.

For obvious reasons, the ideal situation would be the complete elimination of the sample preparation step from the analytical process. However, despite the current degree of development of the analytical instrumentation used for final determination in most instance this is not feasible. Concepts like miniaturisation, integration and simplification became key concepts that have already been proved to effectively contribute to solve some of the drawbacks of conventional sample preparation methods and that, in some studies involving size-limited samples, can probably be considered the best, if not the only, analytical alternatives.

The present review article focuses on sample preparation, with examples primarily related to liquid and solid matrices, and more specifically on selected modern techniques, i.e. those introduced in the last two decades or so. Most recent developments and achievements in the field will be discussed on the basis of representative examples. Attention will focus in the analysis of trace organic compounds due to the difficulty associated to this type of determination. Nevertheless, if relevant, examples will also be taken from other application areas as far as they involved a chromatographic (or closely related separation) step for the final instrumental determination of the target compounds. –Omic sciences remain out of the scope of this review as these studies involve different, but often well defined and established, treatment strategies. In all cases, emphasis will be on techniques that have already demonstrated their practicality by the analysis of real-life samples.

2. Liquid samples

2.1. Solvent-based extraction techniques

LLE has been for years the reference method for the treatment of liquid samples. Some of its most relevant limitations, viz. formation of emulsions, consumption of large volumes of organic solvent and dilution of the analytes, can easily be circumvented by simply scaling down the dimensions of the extraction system. This approach has been used to develop some modern miniaturised extraction techniques that have nowadays achieved a different level of success and acceptance by analysts.

2.1.1. In-vial liquid–liquid extraction

When the volumes of the aqueous sample and the extractant are small enough, LLE can be performed in a chromatographic vial and the analytical approach is called in-vial LLE. The experimental

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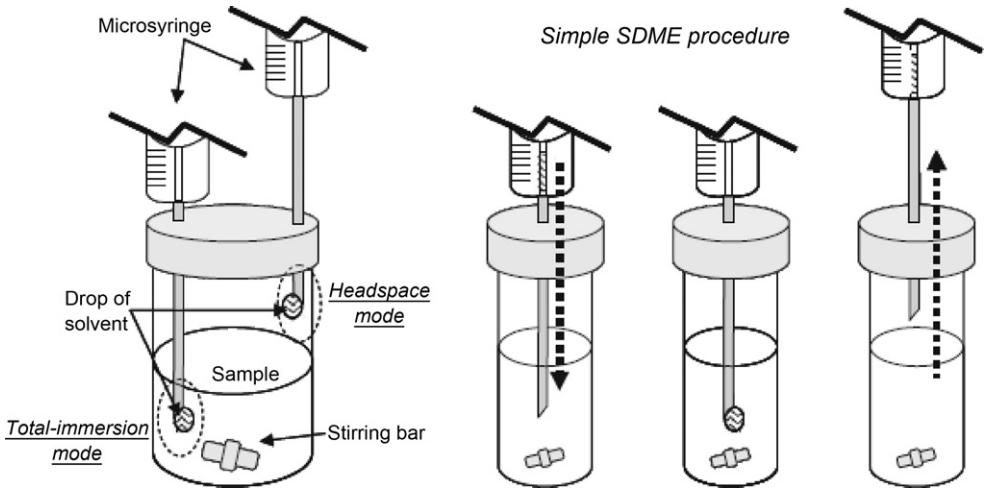

Fig. 1. Basic configurations for SDME and steps in the SDME immersion mode [13].

parameters affecting the analyte partition process, i.e. to be optimised, are similar to those of LLE. Salting out of the mixture and in-vial derivatization of the analytes can also be used to improve the extraction efficiency. However, apart from its simplicity and the significant reduction of the amount of organic solvent(s) used, probably the most interesting features of the technique are the faster separation of phases due to the (virtual) elimination of the emulsions, and the very favourably phase ratio. Together these contribute to increase the efficiency of the extraction process in terms of analysis time and analyte recovery as compared to conventional LLE. In addition, when the resulting extractant is clean enough to avoid compromising the final instrumental determination, the organic phase can be directly sampled by conventional autosamplers and injected into the separation-plus-detection system without any further treatment or concentration. In this case, the complete sample preparation can be done in an unattended manner using any of the commercially available modern multipurpose autosamplers allowing heating and shaking of the vials, automatic dilution, concentration, derivatization, and addition of internal standards, among other operations.

Up to now, in-vial LLE has provided satisfactory results for the fast (semi)-automated extraction of analytes with medium and low polarity from relatively clean aqueous samples [8,9]. Typical experiments involve sample volumes of 1–2 mL and ca. 500 μL of an organic solvent for which the target compounds showed a high affinity. In a typical application study, Abdel-Rehim [10] reported limits of detection (LODs) as low as 10 nmol/L for the amide-type local anaesthetic ropivacaine and bupivacine using only 1.0 mL of human plasma, although in combination with large volume injection (LVI) of 50 μL of the final extract. In general, the use of membranes is recommended in the case of dirty or more complex matrices to reduce the amount of matrix components co-extracted. Otherwise, additional clean-up before instrumental analysis becomes mandatory [11].

2.1.2. Solvent micro-extraction techniques

Several new micro-LLE-based techniques have also been developed during the last 15 years by developing new analytical approaches on the base of previously known concepts or by developing completely new set-ups and techniques. These so-called solvent micro-extraction (SME) techniques have been described and discussed in detail in a number of recent reviews [1,12–18] and books [19]. Different criteria have been used to classify these several techniques. For simplicity, in this review article a terminology and classification essentially based on the number of phases involved in the extraction process and the two basic working modes, direct immersion sampling and headspace (HS) sampling, has been used [19].

The simplest technique belonging to the SME group is single-drop microextraction (SDME) [20,21], in which a single microdrop of a water-insoluble solvent suspended at the tip of a gas chromatography (GC) syringe is either immersed in an aqueous sample or exposed to the HS of a sample contained in a vial (Fig. 1). Typical extractant and aqueous volumes are 1–8 μL and 1–10 mL, respectively. Although SDME is an equilibrium technique, it allows enrichment factors as large as 300 with extraction times as short as 1–15 min. Stirring of the sample (up to ca. 600 rpm to prevent drop dislodgment), salting-out, application of temperature and analyte derivatization (to reduce its polarity or increase its volatility) are common practices that, in general, contribute to increase the extraction efficiency and reduce the analysis time. The simplicity of the analytical procedure, the possibility to perform it manually or (semi)-automatic using an autosampler, and the feasibility of obtaining ready-to-analyse extracts have probably been additional factors contributing to the rapid development and acceptation of this environmentally friendly technique in different research fields.

Direct-immersion SDME has been demonstrated to be useful for the extraction of relatively non-polar and semivolatile analytes from water samples that contain little or no particulate or dissolved matter. However, the analysis of more complex matrices, such a urine, requires a previous filtration of the sample [22]. Due to its characteristics, the technique is particularly suited for the treatment of size-limited samples, as recently demonstrated by Wu et al. [23], who used it for the simple, fast, efficient and inexpensive extraction of three methoxyacetophenone isomers from relatively complex samples (i.e., biological fluids). The analysis, which took only 5 min, involved only 10 μL of sample and 0.5–1.0 μL of organic extractant, and was termed drop-to-drop micro-extraction (DDME). Once optimised, the method showed a linear response in the 0.01–5 μg/mL range, relative standard deviations (RSDs) better than 2.6% ($n = 5$), and LODs of 1 ng/mL using GC–MS/MS for final determination, which demonstrated the feasibility of the technique for the determination of the investigated drugs in blood, serum and urine.

Application of SDME to the analysis of polar compounds required a modification that resulted in a three-phase SDME system named liquid–liquid–liquid micro-extraction (LLLME) [24]. In this approach, the deionised polar analytes were preconcentrated from the aqueous sample in a few microlitres of organic phase placed in a PTFE ring and subsequently back-extracted in an

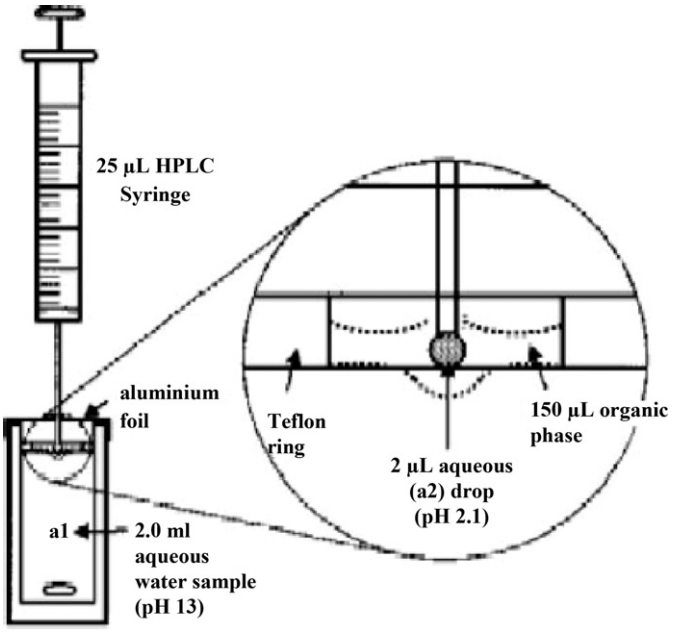

Fig. 2. Basic configuration for LLLME [26].

aqueous micro-drop that acted as receiving phase (Fig. 2). Next, this micro-drop was withdrawn into the syringe and directly subjected to liquid chromatography (LC) or capillary electrophoresis (CE) analysis. Therefore, the organic phase acts as an organic liquid membrane allowing the simultaneous enrichment and purification of the analytes. Its higher stability as compared to the organic drop of the two-phase SDME format allowed higher stirring rates, something that, combined with the small volume of receiving organic phase, resulted in fast extraction processes (ca. 15 min) with higher enrichment factors (in the 200–500 range). The complete renewal of the phases in between extractions also contributed to reduce the risk of cross-contamination, resulted in an improved clean-up of the extracts and higher precision, as recently demonstrated in a typical example dealing with the analysis of narcotic drugs (alfentanil, fentanyl, and sufentanil) in human plasma and urine [25].

SDME can also be accomplished by direct exposure of the drop to the headspace of the investigated sample. In this case, the technique is named headspace single-drop micro-extraction (HS-SDME). This approach can be applied to gaseous, aqueous and solid samples. HS-SDME performs very efficiently for the preconcentration of volatile non-polar analytes, and has the advantage over direct immersion SDME of providing cleaner extracts in shorter analytical times due to the possibility of using higher stirring rates. For the rest, experimental parameters affecting the efficiency of the process are essentially the same as for the immersion mode.

All previously described SDME-based techniques are static and, consequently, the main factor determining both the extraction efficiency and the extraction time is the diffusion of the extracted analytes from the drop surface to its inner part. Although the use of less viscous solvents and higher stirring rates and temperatures can contribute to increase this diffusion rate, constant renovation of the solvent surface by using a dynamic approach is probably a more effective approach. Two type of dynamic SDME are possible: in-syringe and in-needle SME. In the former approach, the aqueous sample or headspace is withdraw into the syringe needle or lumen and ejected repeatedly to perform the desired solvent enrichment [27]. In the in-needle dynamic approach [28,29], around 90% of the extraction drop is withdrawn into the syringe needle and then pushed out again repeatedly for sample exposure. For obvious reasons, the in-syringe approach is more effective when dealing with relatively pristine samples. Meanwhile, the in-needle approach may be more useful for the analysis of relatively dirty samples, i.e., samples containing relatively high amount of matrix components that could affect the subsequent instrumental analysis.

2.1.3. Hollow fiber-protected two-/three-phase solvent microextraction

Hollow fiber-protected two-phase solvent micro-extraction (HF(2)ME) was introduced by He and Lee [21] in 1997 with the name of liquid-phase micro-extraction. In its simplest version, the technique involves a small-diameter microporous polypropylene tube (the hollow fiber), usually sealed at one end, to contain the organic extracting solvent. The open end of the hollow fiber is attached to a syringe needle used to fill the fiber with the organic solvent. Once filled, the fiber is immersed in the vial containing the investigated aqueous sample to allow analytes migration through its walls. After a preselected extraction time, the solvent is withdrawn with the syringe and transferred to the instrument selected for analyte determination, typically GC. HF(2)ME can consequently be considered a liquid–liquid membrane extraction [19] and so it is more appropriate than SDME for the analysis of "dirty" aqueous samples. The use of larger extractant volumes (typically in the 4–20 μL range) and the possibility of applying higher stirring rates are other advantages of HFME over SDME. On the other hand, HF(2)ME usually involves longer extraction times than SDME (20–60 min *vs.* 5–15 min with SDME), and, unless LVI was used, only a fraction of the HF(2)ME organic extractant is transferred to the instrument selected for final determination. In addition, and although it can be adapted for use with an autosampler [30], probably its main limitation is that each individual hollow fiber should carefully be sized and prepared before use [19].

The three phases involved in HF(3)ME are the aqueous sample investigated, the water-immiscible organic solvent that fills the pores of the hollow fiber polymer before this is attached to the syringe needle, and an aqueous acceptor phase that is placed in the lumen of the fiber with the help of the syringe [31]. HF(3)ME is operated in a way similar to HF(2)ME but, since the final acceptor solution is aqueous, the technique is used to extract water-soluble analytes from aqueous matrices, and LC and CE are usually preferred for final instrumental determination of the tested analytes. Similarly to that explained for three-phases SDME, the pH of the aqueous sample and the acceptor phase are key parameters controlling the efficiently of the HF(3)ME process [24,32].

HF(2)ME and HF(3)ME, which can be used in a static or dynamic mode similarly to that described for SDME, share their most pressing shortcomings, namely relatively long extraction times, difficulty of complete automation and intensive manual preparation of the fiber before use. However, a number of examples can be found in the literature proving the practicality of the approach for the preconcentration of analytes of divergent polarity from size-limited aqueous samples. Interestingly, this process can be favoured by the application of a potential difference between the two phases [33]. In this case, the technique is referred as electromembrane extraction (EME).

In an attractive modification, the fiber, filled with solvent, is sealed at both ends, which allows to place it directly into the stirred solution for extraction. In this case, after a preselected extraction time, the fiber it retrieved from water and the enriched solvent is removed by puncturing the fiber with a chromatographic syringe. This technique is called solvent bar micro-extraction (SBE) [34] and can also be used as a two- or three-phase system.

2.1.4. Dispersive liquid–liquid micro-extraction

The dispersive liquid–liquid micro-extraction (DLLME) was introduced in 2006 by Assadi's group [35] and can be considered a modification of the miniaturised LLE. In this technique, a relatively

Table 1
Selected applications of DLLME.

Sample	Analyte	Extraction solvent (μL/mg)	Disperser solvent (mL)	Extraction time[a] (min)	LOD (μg/L, ng/g)	Ref.
Water	PAHs	Tetrachloroethylene (8)	Acetone (1.0)	2	0.007–0.03	[35]
Water samples	Chlorophenols	Chlorobenzene (10)	Acetone (0.5)	2	0.010–2.0	[37]
Water samples	Phthalate esters	[C8MIM][PF6] (32)	Acetonitrile (0.75)	10	0.68–0.36	[38]
Water samples	UV filters	Chlorobenzene (60)	Acetone (1.0)	3	0.002–0.014	[39]
Soil extract	Pesticides and metabolites	[HMIM][PF(6)] (117.5)	Methanol (418)	10	0.2–90	[40]
Marine sediment extract	Organophosphorus pesticides	Carbon tetrachloride (17)	Acetonitrile (1.0)	2	0.001–0.009	[41]
Soil extract	PCBs	Chlorobenzene (30)	Acetone (1)	3	0.02–0.05	[42]
Centrifuged apple juice	24 multiclass pesticides	Carbon tetrachloride (100)	Acetone (0.40)	3	0.06–2.2	[43]
Banana extract	8 multiclass pesticides	[HMIM][PF_6] (88)	Methanol (0.71)	20	0.32–4.7	[44]
Milk	3 phenylurea pesticides, 4 triazines	[HMIM][PF_6] (60)	–	7	0.46–2.0	[45]
Extracted and purified milk extract	8 PCBs, 6 PBDEs	Chlorobenzene (19)	Acetone (1.0)	NS	0.01–0.4	[46]
Extracted and purified food extracts (milk, egg yolk, olive oil)	Cholesterol	Carbon tetrachloride (35)	Ethanol (0.8)	1–2	0.01	[47]
Extracted and purified porcine tissue	Clenbuterol	Tetrachloromethylene (150)	Ammonia (0.005)	5	0.07	[48]

[a] This time refers strictly to the time required to complete the DLLME process. That is, it does not include the time required for previous treatments in the case of solid matrices.

small amount of a water-immiscible extraction solvent (typically 10–50 μL) is dissolved in 0.5–2 mL of a water-soluble solvent and rapidly injected with a syringe into the investigated aqueous sample (up to 10 mL). The fast injection of the mixture of organic solvents into the water causes the water-immiscible solvent to be dispersed in the aqueous mass as small micro-drops in which the target analytes are rapidly extracted. The enriched organic phase is then separated from the aqueous sample by centrifugation or frozen (depending on its density) and directly subjected to instrumental analysis, typically by GC. Application to polar analytes requires previous pH adjustment and/or in situ derivatization, which can be accomplished by either direct addition of the derivatization agent to the sample or by dispersion together with the extraction solvent.

The several manual manipulations involved in DLLME made the technique difficult to automate and the use of internal standards and surrogates even more necessary than for previously revised SME-based techniques. Despite these shortcomings, many examples of application of DLLME to the determination of analytes of different polarity in aqueous samples or extracts can be found in the literature (see, e.g. [36] and references therein), which is considered a demonstration of the rapid acceptance that this green, fast and efficient (enrichment factors in the 100–900 range) extraction technique has experienced since its introduction. Table 1 summarises some selected applications studies involving DLLME and highlights representative trends in this field.

DLLME was primarily applied to the determination of non-polar analytes in pristine aqueous samples [35]. However, the technique was rapidly extended to polar analytes by their in situ derivatization during DLLME [37] or, more recently, by using ionic liquids as extractant [38]. For aqueous matrices, equilibrium is achieved instantaneously [35]. Phase separation by centrifugation, which typically takes 2–20 min, or alternatively manual removal of the frozen drop, become the most time consuming step of the treatment protocol.

The analysis of solid matrices is only possible after extraction of the target analytes from the matrix and dilution of the extract in water. Therefore, in this type of application, DLLME is essentially used for preconcentration and/or purification of the target analytes rather than as a real extraction technique. Ravelo-Pérez et al. [44] used this approach for the determination of eight pesticides belonging to different classes from bananas. The optimised method started with the extraction of the homogenised fruit sample (1 g) with acetonitrile. After evaporation and reconstitution of the extract in 10 mL of water, the target compounds were preconcentrated by DLLME using [HMIM][PF6] (88 mg) as extractant and methanol (714 μL) as disperser solvent. The ionic liquid was recovered after centrifugation at 4000 rpm (20 min), diluted in acetonitrile and analysed without any further treatment by LC-DAD. Acceptable mean recoveries in the 53–97% range, with RSD values lower than 9%, and LODs (0.32–4.7 μg/kg) below the maximum residue levels (MRLs) set in current legislations were obtained for all target analytes. These analytical figures of merit would demonstrate the validity of the optimised method for the intended determination, although the observed severe matrix effect made the use of matrix matched calibration mandatory.

In most applications dealing with DLLME of (semi-)solid samples, the target analytes are extracted by shaking of the investigated matrix with an appropriate extraction solvent. However, the efficiency and speed of this treatment can be increased by using more selective techniques, such as supercritical fluid extraction (SFE) [41], or by applying auxiliary energy to the extraction vessel, e.g. microwaves [45] or ultrasound [40,48]. The latter were preferred by Liu et al. [48] for the extraction of clenbuterol from porcine tissue. In this study, 1-g tissue sub-sample was put into a 5 mL conical tube and sonicated for 10 min with 2 mL of anhydrous alcohol as extraction solvent. This extraction step was repeated in three times. Supernatants were separated by centrifugation at 16,000 rpm for 5 min, combined and defatted with hexane, which was subsequently removed by centrifugation at 4000 rpm for 5 min. After concentration, the fat-free extract was transferred to a PCX cartridge for further clean-up. Clenbuterol was eluted from the solid phase extraction (SPE) cartridge with 5 mL of methanol:ammonia (95:5, v/v). This clean extract was concentrated to 0.5 mL and diluted with water. Then, ammonia (50 μL) and tetrachloromethylene (150 μL) were added and the mixture was ultrasonicated for 2 min to get the fine cloud solution. After phase separation by centrifugation at 4000 rpm for 5 min, the sediment phase was evaporated to dryness and reconstituted in 20 μL of mobile phase for further LC analysis. The method showed a good linearity (r^2 = 0.9995) in the 0.19–192 μg/kg range, and provided recoveries better than 88% with RSDs below 4%. The LOD was 0.07 μg/kg, which was below the MRLs established by FDA and WHO for samples incubated for 30 days. Fig. 3 shows a typical chromatogram obtained for porcine meat. The clearer chromatograms observed when applying the proposed SPE-DLLME procedure (compared with SPE) demonstrated the selectivity of the sample treatment process.

The wide variety of SME techniques available nowadays sometimes makes it difficult to determine which can be the most suitable

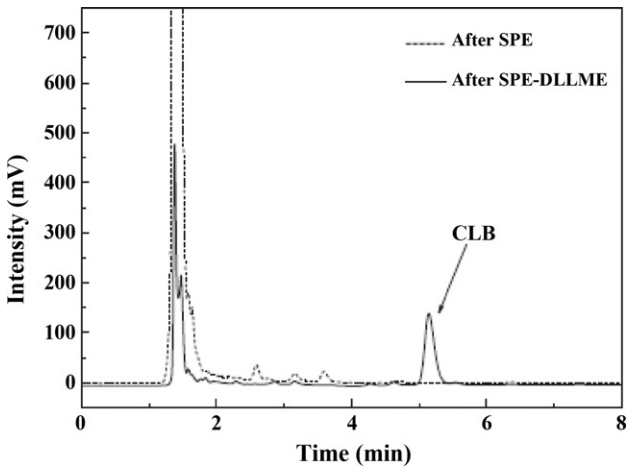

Fig. 3. Comparison of the HPLC-UV–vis chromatograms obtained for porcine meat with SPE and SPE-DLLME [48].

alternative for a particular application. The flowchart shown in Fig. 4 could be a useful tool for this purpose.

2.2. Sorption-based extraction techniques

Many techniques currently in use for pretreatment of gaseous, fluid or liquid samples are based on trapping the investigated analytes on, or in, a suitable sorbent. The preconcentrated test compounds are subsequently desorbed, in a more or less selective fashion, by elution with a relatively small amount of solvent either in a vial or in an appropriate interface; or by thermal desorption, typically in the injection port of the instrument selected for final determination. The later approach avoids dilution but is obvious limited to (semi-)volatile thermally stable compounds.

In general, techniques based on sorption extraction can nowadays be considered well established and accepted. In fact, some of them are among the most widely used in analytical laboratories. As expected for a mature techniques, in most instances no major conceptual changes have been introduced during the last decade and as with other techniques, instrumental developments have mainly been orientated to increase automation and integration of the techniques with final instrumental analysis (a field where miniaturisation has again played a relevant role). Thereby, the most active research topics concerning these techniques have been the synthesis of new sorbent phases that solved the remaining practical problems in this research field and the development of novel application studies.

2.2.1. Solid-phase extraction

SPE is probably the most widely accepted technique for preconcentration and clean-up of analytes from fluids and aqueous samples. The large variety of sorbents commercially available makes this technique suitable for the determination of analytes with divergent chemical structures and polarities. As a result current research into sorbents focuses mainly in the development of novel sorbents allowing higher loading capacities, higher efficiency for retention of highly polar analytes from aqueous matrices, and in the synthesis of class-selective immuno-sorbents (ISPEs) and molecular imprinted polymers (MIPs) allowing an improved selectivity during the retention process and so contributing to the simplification of the subsequent clean-up and/or detection steps [49,50]. As an example, in a recently published study, five ionic liquid-modified porous polymers with different imidazolium-based functional groups were obtained and a new molecular imprinting technique was introduced to form the ordered functional groups in the porous structure [51]. The sorbent finally selected allowed selective SPE of tanshinones from functional drinks.

The progress achieved in past decades in the synthesis of sorbent materials has enabled very pure small-size sorbent particles to be obtained in a very reproducible way. These small particles (ca. 40 μm) provided higher retention capacities than conventional-size ones, an interesting feature that promoted the use of smaller SPE cartridges without a significant lost of retention efficiency. Reducing the size of the conventional 1–6 mL SPE syringe barrels to the 10 mm × 1–2 mm i.d. of the so-called Prospeckt-type cartridges used in the hyphenated systems led to a reduction of sample volumes from 0.5–1.0 L to less than 50–100 mL. Actually, quite often, even 5–10 mL suffices to obtain similar LODs of 0.01–0.1 μg/L with SPE-LC and 1000-fold lower with SPE-GC that previously required 100-fold larger volumes. More importantly, quantitative elution of the analytes can be achieved with 50–100 μL of the appropriate solvent, i.e. with a volume small enough to allow complete transfer

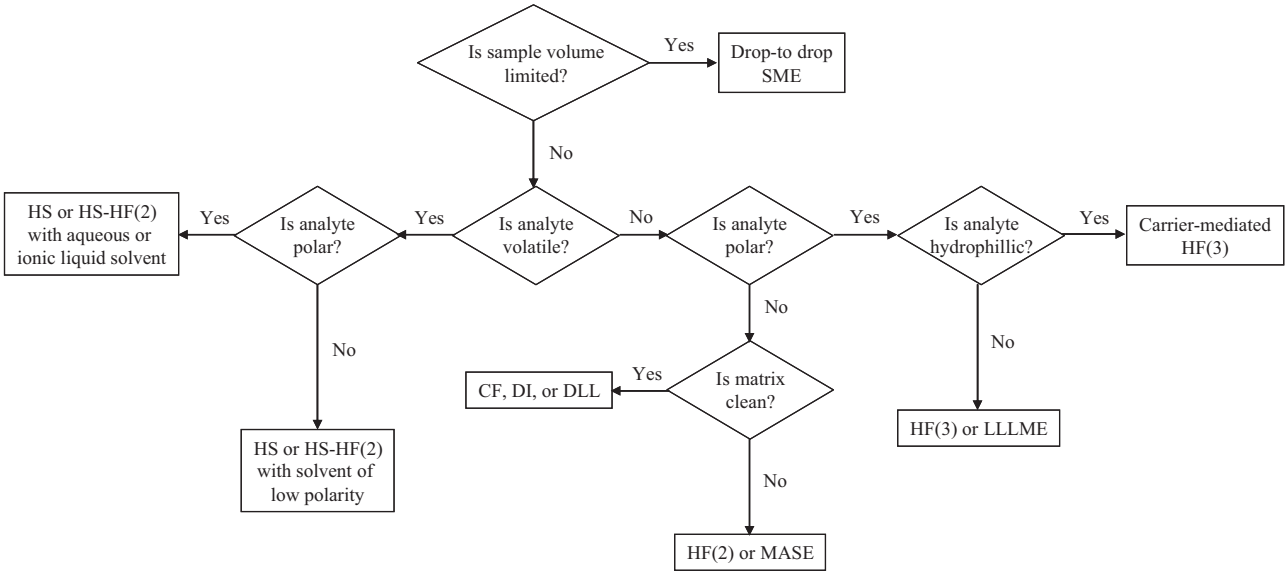

Fig. 4. Flowchart for SME mode selection [19]. CF, continuous flow; MASE, membrane-assisted solvent extraction. For other acronyms, see text.

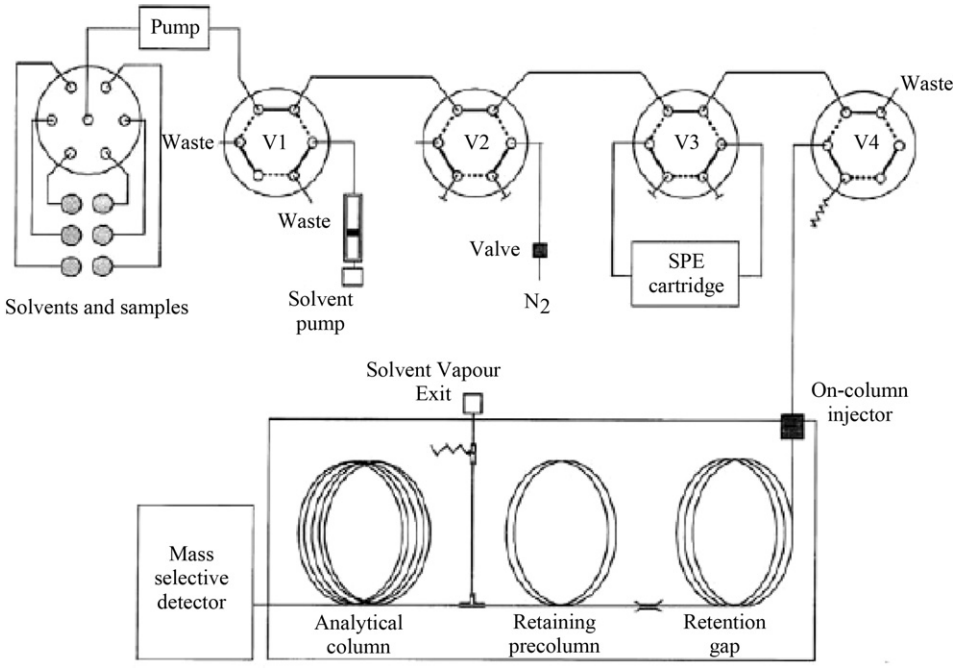

Fig. 5. Scheme of on-line SPE-GC–MS system [53].

to the instrument selected for final determination. This fact promoted the development of hyphenated and automated systems for unattended, green and fast (ca. up to 20 min) treatment of aqueous samples with minimal sample and solvent consumption and significant reduction of waste generation [52]. A scheme of an on-line SPE-GC–MS system is shown in Fig. 5.

The experimental parameters to consider during method development in this type of valve-based hyphenated SPE systems are the same as for conventional (large scale off-line) SPE, namely the nature and amount of sorbent, the nature of the solvents used in the different SPE steps and, in particular, their flow rates. The main problems yielding low analyte recoveries are usually also similar: reduced sorbent capacity or too strong retention, slow kinetics of the sorption process (or, in other words, a too high sample and/or solvent flow rates), and a possible adsorption of the analytes onto the tube used to connect the different parts of the system. On the other hand, in these closed systems the risk of analyte degradation and oxidation is greatly reduced as compared to the (open) conventional approaches and due to the shorter analytical times, method development should be faster. Finally, the exposure of operator to hazardous solvents is greatly reduced.

Accepting that the hyphenation of SPE with LC and GC can nowadays be considered achievable goals, at present, development in this area is mainly orientated to the progressive reduction of the sample amount required for accurate determination of trace compounds and to the further simplification of the sample treatment methodologies. Both aspects usually rely on the use of any of the currently available high-capacity or highly selective sorbents and/or the use of very powerful MS- [54] or, preferably, MS–MS [55]-based detectors. Such approaches have been demonstrated to be useful for extremely fast determinations that could be carried out with much lower analysis times than those required by conventional SPE. For example, replacing the SPE-LC part of the system by a single short column, SSC (1–2 cm length), and using MS–MS as detection system allowed the study of real-time analyte degradation at the trace level [55,56], with LC run times of, frequently, only some 3 min. A slight modification of the conventional valve configuration typically adopted for miniaturised SPE to introduce a filter before the SPE cartridge allowed the direct injection of soil and sediment slurries in the SPE-GC–MS system. This set-up allowed in-deep evaluation of the so-called fast adsorption of pesticides in these complex matrices by simultaneous analysis of both phases (i.e., water and soil/sediment particles) in less than 45 min and with a single injection of the mixture in the system [57]. Finally, the progressive reduction of the sample size required to perform these types of hyphenated analyses has made possible, in some cases, the direct injection of the aqueous sample [58] or of the aqueous extract obtained from fruits and vegetables [59], with LODs low enough to consider the methods appropriate for the fast screening of selected relevant pesticides. However, in such applications, the use of a highly selective and sensitive detector, such as MS–MS, now becomes mandatory. In the case of the GC coupling, these trends have promoted an important development in the field of LVI. Some of the novel LVI interfaces [60,61] allow direct water injection in the GC, and the introduction of up to 10 mL of solvent using the slow injection mode or multiple fast injections in a packed liner. Nevertheless, the practicability of these approaches in the different application areas look to be strongly dependent on the type and concentration of the interferences present in the sample.

Up to now, and somehow surprisingly due to their many attractive features, the number of studies involving the use of SPE disks in hyphenated SPE-LC and SPE-GC has been rather limited [62]. Resin disks (0.7 mm diameter) have also been mounted inside the removable needle chamber of a 50 μL Hamilton gas-tight syringe. This set-up was demonstrated to be a valuable miniaturised automated alternative that enabled the efficient preconcentration of substituted benzenes from a volume of water as small as 2.5 mL. The method provided recoveries higher than 90% at the 10 ng/mL level with GC-FID and required only 5 μL of acetonitrile for desorption [63].Other SPE formats, such as 96-well-plate, although popular in certain application areas, e.g. high throughput clinical analysis, are still rarely used in other research fields, in which they are far from been considered really established and accepted configurations.

2.2.1.1. Micro-extraction in packed syringe. The previously mentioned approach involving packing of resin disks in a GC syringe could be considered the precedent of a recently introduced

Table 2
Comparison of QuEChERS method with magnetic MIP with the results obtained by using MIP-SPE and MIP-SPME for the determination of tetracycline antibiotics.

Method	Sample preparation time	Analytical technique	Recovery (%)	Precision (RSD, %)	LOD (ng/g)	Reused of polymer (times)	Ref.
Magnetic MIP	15 or 20 min (simultaneous extraction + clean-up)	LC–MS/MS	73–96	31–2	0.06–0.19	10	[73]
MIP-SPME	5 or 10 min for homogeneity + 10 min for centrifugation + 30 min for SPME clean-up	LC-fluorescence	72–94	3–6	1.5–3.5	100	[77]
MIP-SPE	1 min for homogeneity + 30 min for centrifugation + several tens minutes for SPE clean-up	LC-UV	66–69	<8	Not mentioned	Not mentioned	[78]

Adapted from [73].

sorbent-base technique, the so-called micro-extraction in packed syringe (MEPS). MEPS is a miniaturised SPE techniques in which a sorbent packing material (ca. 1 mg) is placed at the top of the syringe needle. For extraction, 10–250 μL of an aqueous sample is successively withdrawn and ejected so allowing preconcentration of the analytes on the selected sorbent. Analytes elution is typically accomplished with 20–50 μL of an appropriate solvent, which can directly be transferred to the GC/LC port. MEPS applications include the determination of PAHs in water [64] and of drugs in blood [65], among others [66].

2.2.2. Dispersive solid-phase extraction

Probably the most successful development introduced in the last years in the field of SPE has been the method known as QuEChERS. The acronym applies for Quick, Easy, Cheap, Rugged, Effective and Safe, which is supposed to describe the main merits of the analytical procedure introduced by Anastassiades et al. in 2003 for the determination of pesticides in fruits and vegetables [67]. The method is a multi-step procedure based on dispersive solid-phase extraction (d-SPE). In its basic scheme for pesticide analysis in fruits and vegetables, the method involves the initial sample treatment with magnesium sulfate to promote water separation from the organic solvent, followed by treatment with primary secondary amine (PSA) sorbent to remove polar components, such as organic acids, some sugars and polar pigments. Other protocols include sample shaking with graphitised carbon black to eliminate sterols and pigments like chlorophyll. The rapid acceptation of this fast and efficient sample preparation protocol promoted its quick adaptation for other types of analysis, including such different application as the determination of non-polar microcontaminants [68,69] and acrylamide in different food items [70], or drugs in animal tissues [71] and blood [72].

d-SPE has also taken advance of advances in the field of new materials. Chen et al. [73] prepared a magnetic molecularly imprinted polymer for the separation of tetracycline antibiotics from egg and tissue samples by d-SPE. The satisfactory results obtained with this method as compared to more conventional configurations such as MIP-SPE and MIP-SPME (Table 2), together with the simplicity of the operation methodology and the possibility of recovering the magnetic particles with a simple magnet, make of this novel approach an interesting alternative for sample preparation in other application fields.

A miniaturised version of d-SPE has recently been introduced and named disposable pipette extraction (DPX). The basic concept is similar in both techniques, but in DPX the sorbent is contained inside a disposable pipette tip in which the sorbent–analyte interaction is improved by turbulence The technique is fast, simple, involves minimum reagent consumption, full-fills the principles of green sample preparation, and has already demonstrated its feasibility for a number of applications, including pesticide determination in fruits and vegetables [74], drugs in vitreous humor [75] and explosives and gunshot residues [76].

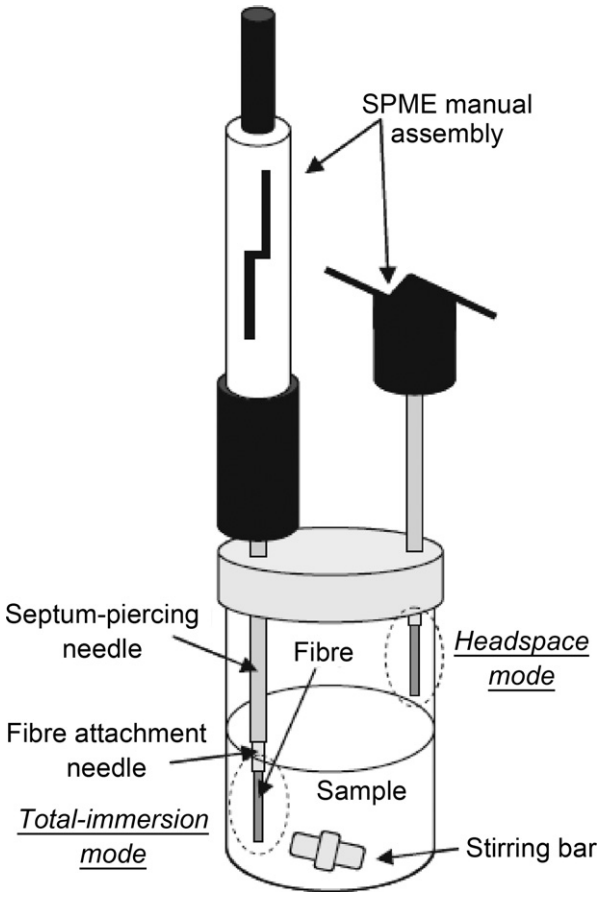

Fig. 6. Basic configurations for SPME [13].

2.2.3. Solid-phase micro-extraction

Solid-phase micro-extraction (SPME) was introduced in 1990 by Pawliszyn's group [79] as a (virtually) solvent-free preconcentration technique in which the analyte(s) is(are) adsorbed onto a fused-silica fiber coated with an appropriate sorbent layer by simple exposure of the fiber for a pre-selected time to the headspace of the sample or by direct immersion in a liquid sample (Fig. 6).

Despite been an equilibrium (i.e., non-exhaustive) technique and the initial limitations regarding the nature of the commercialised sorbent coating, SPME was rapidly accepted as a simple, reproducible, miniaturised and green technique, and its feasibility for fast and accurate analysis of compounds of different nature

was illustrated through a number of application studies [80–82]. Today, on-line coupling of SPME with LC and GC have been achieved and a number of systems (e.g., autosamplers) allowing complete automation of the process are commercially available. Alternative SPME-formats have also been proposed [83,84] although, in general, they have achieved a much more limited success.SPME can be considered a well established and widely accepted technique and current research in this field focuses mainly on the development of new coatings and novel analytical strategies that contribute to improve the sensitivity of the technique.

The variety of commercially available fiber coatings has increased significantly during the last year, something that has contributed to expand the range of analyte classes that can be successfully analysed. Today, in addition to the originally introduced non-polar PDMS, semi-polar polydimethyl siloxane–divinylbenzene (PDMS–DVB), polar polyacrylate (PA), Carbowax–divinylbenzene (CW–DVB) liquid-like phases, coated porous particle phases such a polydimethyl siloxane–Carboxen (PDMS–Carboxen), poly(3-methylthiophene) and Nafion are available. Other less frequently used coatings include carbon nanotubes [85], several crown ethers [86], MIPs [87], anodized metals [88] and ionic liquids [89]. The use of selective sorbents, such a MIPs, contributes to increase the selectivity of the process, which results in a significant reduction of the need for previous fractionation and purification steps in the analysis of complex extracts and minimise the risk of instrument contamination [13].

Strategies involving the derivatization of the analytes in the aqueous phase have extended the range of application of SPME to very polar [90] or ionic substances [91,92]. Applications involving on-fiber derivatization require conversion of the analytes after extraction by applying the reagent as a gas and are, as far as we know, still scarce in the literature. The relatively high RSD values typically associated to this approach (e.g., 10–35% for chemical warfare agents at 1–20 μg/mL levels, $n = 6$ [93]) can be regarded as an indicator of conditions which are difficult to control.

Generally speaking, although the analysis of aqueous samples can be accomplished without (or with little) pretreatment, SPME of target compounds from more complex (solid) matrices typically requires a previous separation of the analytes from the main matrix components [94], uses longer extraction times and is frequently less exhaustive than for liquid samples because of the less favourable extraction conditions.

Finally, among the recent developments in the field of SPME, a new system should be highlighted that allows cooling on the upper part of the sample vial and simultaneous heating and ultrasonic extraction of the bottom part of the vial (Fig. 7). The system has been applied to the HS-SPME with a 100 μm PDMS fiber of compounds with medium volatility, such as polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzo furans (PCDFs), from soil slurries.

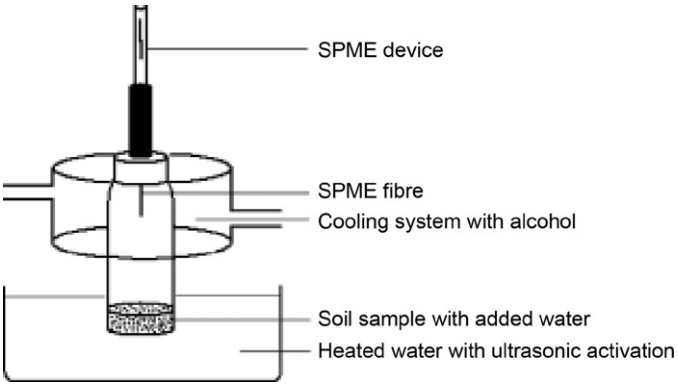

Fig. 7. Scheme of the SPME-based system [95].

Although the use of GC–MS/MS and appropriated internal standards were mandatory, the feasibility of the approach for fast screening of some types of heavily contaminated samples was demonstrated [95].

2.2.4. Stir-bar-sorptive extraction

In a typical stir-bar-sorptive extraction (SBSE) experiment, a magnetic stir bar coated with 55 or 219 μL PDMS (corresponding to magnets 10 and 40 mm long, respectively) is spun into an aqueous sample (or extract) for a selected, and often fairly long, extraction time [96]. SBSE of the headspace of a gas, liquid or solid sample contained in a sealed vial is also possible, although less frequently used. The magnetic stir-bar can also be inserted into a short length of PDMS or silicon tubing. Irrespective of the format, the surface area of the stir bar is greater than that of the SPME fiber. The volume of the adsorbent is also increased at least by a factor of 100, which results in a higher phase ratio than in SPME and, hence, a higher extraction efficiency and lower LODs. Once the extraction step is completed, the stir bar is removed, often manually, and transferred to either the injection port of a GC for thermal desorption [97], or into a solvent for LC analysis [98,99]. As for SPME, in the former approach, all preconcentrated analytes are (virtually) transferred to the instrument selected for final determination; in the latter, only a fraction of the concentrated extract is usually introduced in the LC system. Nonetheless, a novel desorption unit enables fully automated analysis of 98 or 196 PDMS-coated stir bars [100].

A number of studies have demonstrated the feasibility of SBSE for the preconcentration of analytes with medium to low polarity and divergent volatility from essentially aqueous samples (or extracts) [101–103], and the several advantages of SBSE as compared to SPME in most of these applications [104,105]. However, the technique has not been as widely accepted as could be anticipated, probably due to the limited number of coatings materials commercially available and the difficulty of full automation. At present, efforts in this field focuses on the development of dual-phase/hybrid twisters, in which the conventional PDMS phase is combined with another sorbent to increase the selectivity and/or efficiency of the extraction process [106,107], as well as in the development of alternative new coating materials with improved analytical features [108,109].

Finally, it is worth mentioning that due to its particular features, and similarly to SPME, SBSE can be use as a convenient sampling system which can be easily transported for subsequent laboratory analysis or, even better, for on-site determination of the target compounds when combined with portable and miniaturised instrumentation [110].

3. Solid samples

As previously mentioned, the first step in the analysis of semi-solid and solid samples is usually the exhaustive extraction of the target compounds from the matrix in which they are entrapped. The essentially non-selective character of this initial treatment makes mandatory the subsequent purification of the obtained extract, firstly by the rough elimination of chemically non-related main matrix components (e.g., organic matter, lipids, proteins, etc.) and, then, if required, by removal of other chemically related analytes that could interfere in the final instrumental determination of the investigated compounds. Techniques reviewed in previous sections for liquid samples can be used for these purification steps. However, the initial extraction step requires the use of different analytical techniques.

SLE and Soxhlet extraction are well known and accepted techniques for the treatment of (semi-)solid matrices. Despite their limitations, namely they are large scale techniques involving the

use of large amounts of sample and organic solvents, much manual manipulation of the sample and extracts and (virtually) impossible to automate, they have remained essentially unmodified for more than a century [111–113] and are still widely accepted for routine analysis and as reference techniques. Supercritical fluid extraction (SFE) is a long established method, which have been used industrially for many years. However, it was not until an interest was shown in supercritical fluids as chromatographic medium that it started to be seriously investigated as an extraction technique on an analytical scale [14]. Despite the initial promising results, which were summarised in a number of reviews and books [114–116], the use of this technique has slowly decreased during the last 15 years. The problem posed by the relatively low polarity of the most commonly used fluid, carbon dioxide, which made SFE unsuitable for most pharmaceutical and drugs analysis; and the difficulty of handling liquids such as biological fluids, which need to be immobilised on a solid support material, can be suggested as initial reasons of this decline. Since the mid-1990s, the development of more competitive, versatile and less expensive techniques based on the use of pressurised fluids as extractants, including water, contributed to reduce the general interest on this technique. Therefore, although SFE is still considered an interesting extraction technique with some unique features, at present, research in this field essentially focuses on the development of new application studies that have been discussed in detail in texts of a more specialised nature (see, e.g. [117]).

3.1. Matrix-solid phase dispersion

Matrix solid-phase dispersion (MSPD) is a widely accepted technique for the treatment of liquid, viscous and (semi-)solid samples. In MSPD, the extraction and (preliminary) clean-up of the target analytes is carried out in a single step and in a column format. The column configuration simultaneously contributes to simplify the analytical process and avoids the emulsion problems associated with most of the conventional LLE-based procedures. The key parameters controlling the efficiency of the MSPD process are the sorbent dispersant and the extraction solvent protocol. When they are properly selected, MSPD can yield ready-to-analyse extracts that are, in most cases, analysed by GC or LC. The several steps involved in the development of an MSPD method are graphically described in Fig. 9, parts A–E (see below).

In general, the support materials used in MSPD are similar to those used in SPE. Thereby, particle sizes in the 40–100 μm range offer a good compromise among the need of a large surface area for improved sample dispersion and solvent contact, the cost of the solid support and the risk of restricted flow or column clogging that can result from the use of smaller particle sizes (3–10 μm). The use of sorbents with smaller particle size have been reported in the literature, although mainly associated to miniaturised MSPD approaches [118,119]. The amount of sorbent used must ensure proper sample disruption and homogenous dispersion of the matrix components on the material surface. Sample:sorbent ratios of 1:1 to 1:4 have been used in a large majority of the reported MSPD applications [120–122]. Nevertheless, exceptions can also be found in the literature [123] indicating that each sample–sorbent pair should carefully be optimised on the base of the particular goal of each study.

Depending on the elution protocol, complete drying of the final sample–sorbent material to be packed in the column can be necessary. This requirement, most frequent in GC applications where non-polar solvent(s) are used as eluents, can easily be achieved by adding a drying agent, such as sodium sulfate, to the MSPD mixture.

Up to now, lipophilic reversed phase bounded materials have been the most widely used for MSPD [120–122], with a clear preference for C8 and C18. The initially predominant application of MSPD for treatment of biological and food samples (i.e., fat containing matrices) can be suggested as a possible explanation. Nonetheless, examples dealing with the analysis of environmental samples, such indoor dust [124], involving C18 as solid support can also be found in the recent literature.

The reversed phase materials allow efficient retention of medium- and non-polar matrix components on the solid support. Nevertheless, the relatively efficiency of the several commercially available phases for a particular application should better be determined experimentally due to the sometimes dramatic effect of matrix components on the dispersion and fractionation process [118].

Normal phase inorganic materials, i.e. bare silica, Florisil and alumina, disrupt sample structure in a similar way to reversed phase bounded supports, but chemical interaction of the analytes with the solid surface is less extensive than in the latter supports. Celite, sand and diatomaceous earth are able to disrupt the sample structure yielding a homogenous dry power with adequate chromatographic characteristics, but in these cases the selectivity of the MSPD process will depend on the selected elution protocol [125].

When the collected extracts are not cleaned enough (or the separation-plus-detection technique selective enough), some extra purification step(s) should be incorporated to the sample preparation protocol. These treatments can be carried out off-line [126] or, more interestingly, on-line or in-line with the MSPD process. Regarding the latter approach, additional clean-up of the MSPD eluates can be accomplished by, for example, washing of the packed matrix-sorbent mixture with a selected solvent for selective removal of interferences before analyte collection [125,127], or by packing of an extra sorbent layer at the bottom of the MSPD column [128,129]. In the latter case, the chosen sorbent should perform the selective retention of the interfering components washed from the MSPD mixture with the eluent without affecting the target analytes which should pass through this phase unaltered. Fig. 8 shows an illustrative example of the different degree of clean-up achieved when applying some of these different strategies to the analysis of pesticides in single insects, i.e. 40 mg *Porcellio scaber* [127].

Current trends in MSPD focus on the use of novel [130] and/or highly selective materials [131] as dispersants, the miniaturisation of the process [118,119] and/or the combined use of MSPD with one or several of the previously described novel sample preparation techniques to improve the efficiency and/or selectivity of the MSPD process. In an illustrative example, Yan et al. [131] proposed the use of a new synthesised kind of aniline-naphthol molecularly imprinted microspheres (0.2 g) selective for Sudan dyes as

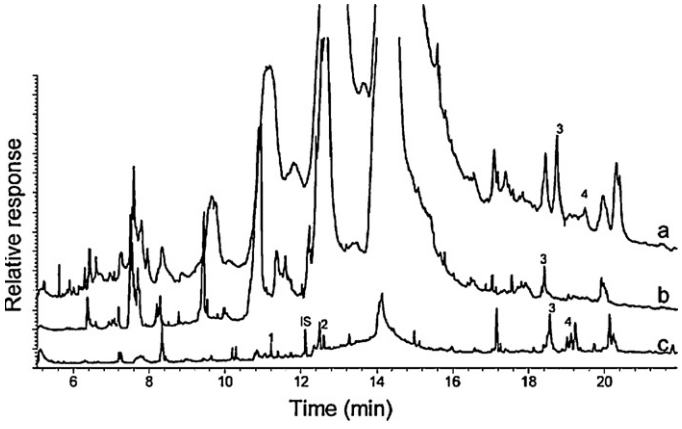

Fig. 8. Comparison of GC–MS chromatograms obtained by MSPD of 40 mg *Porcellio scaber* with 100 μL of (a) ethyl acetate from a C8-bonded silica/sample mixture, (b) ethyl acetate from a C8-bonded silica/sample mixture and washing before extraction, and (c) n-hexane from silica/sample mixture. Peak identification: (1) diazinon, (2) malathion, (3) permethrin, (4) cyfuthrin and (IS) parathion-methyl [127].

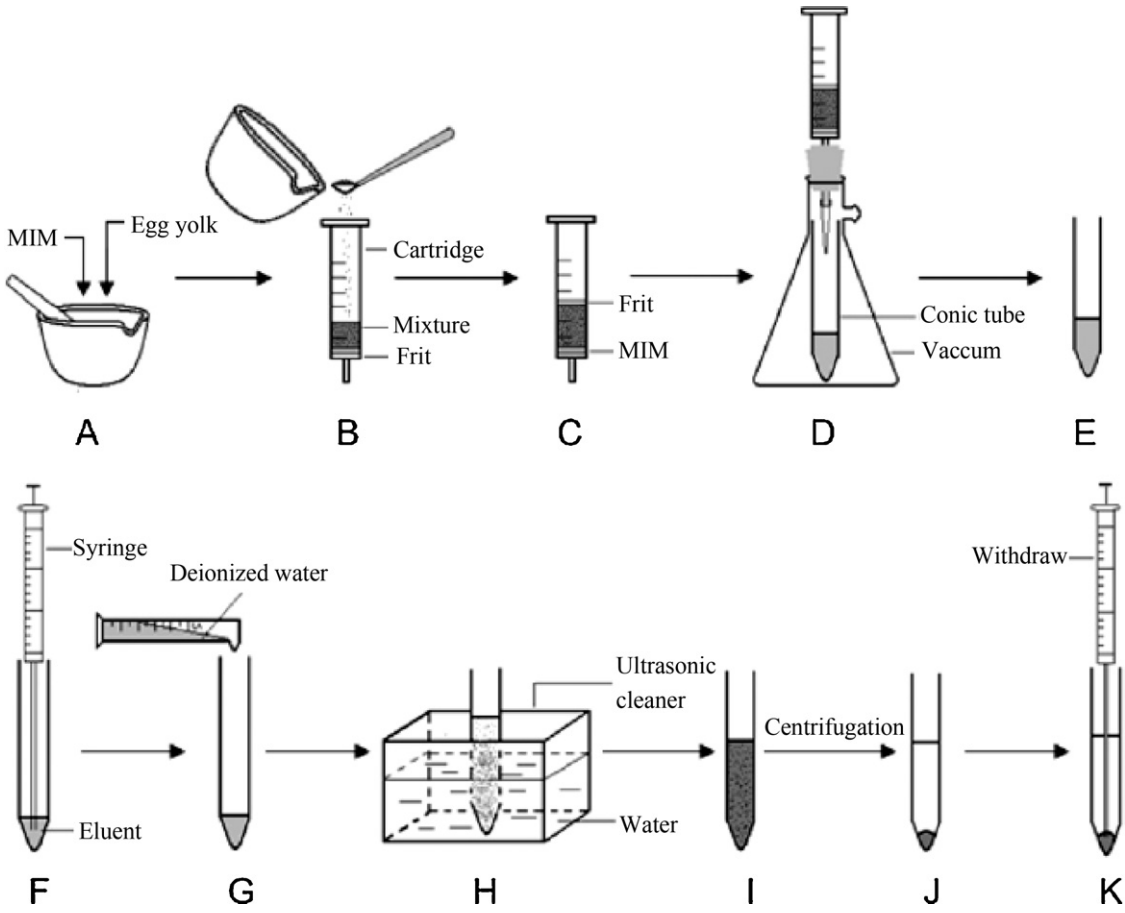

Fig. 9. Schematic of the MIP/MSPD combined with DLLME proposed for the simultaneous determination of four Sudan dyes in egg yolk. (A) Blending of the sample with the selective MIP (MIM); (B) transfer of the blended sample to the column; (C) completed MSPD column; (D) washing of the MSPD column and elution of the test analytes; (E) eluent to be evaporated; (F) injection of the extractant into the eluent for DLLME; (G) addition of deionised water into the DLLME extractant-dispersant mixture; (H) formation of the emulsion assisted by ultrasounds; (I) emulsion of the ternary mixture; (J) phase separation by centrifugation; (K) collection of the high-density extractant [131].

dispersant for miniaturised MSPD of 0.1 g of egg yolk. After washing the MSPD column with 4 mL of methanol:water (1:1, v/v), analytes were quantitatively extracted with 3 mL of acetone:acetic acid (95:5, v/v). The concentrated eluent (1 mL) was used as dispersive solvent for DLLME. The mixture was shaken and sonicated to form a homogeneous cloudy solution and subsequently centrifuged at 4000 rpm for 10 min for phase separation. The four studied Sudan dyes were simultaneously determined by LC-UV after concentration of the corresponding enriched phase. Fig. 9 shows a schematic diagram of the complete sample preparation procedure. The method showed a good linearity for all target analytes in the investigated 0.02–2.0 μg/g range ($r^2 \geq 0.9990$), with recoveries better than 87% and RSDs below 6%.

3.2. Enhanced solvent extraction techniques

Extraction efficiency can be enhanced by heating or shaking a sample, or by using a fluid or solvent with a high diffusion rate [16]. The latter is the basis of SFE, pressurised liquid extraction (PLE) and subcritical water extraction (SWE), while the former approaches are used in microwave assisted extraction (MAE) and ultrasonic extraction.

3.2.1. Pressurised liquid extraction

In a conventional PLE, the sample, typically dispersed in a drying or inert sorbent, such as sodium sulfate, Hydromatrix, or diatomaceous earth, is packed in a stainless-steel cell and, once inserted in a closed flow-through system, extracted with the selected solvent at temperatures above its atmospheric boiling point (up to ca. 200 °C). Because the solvent must be kept liquid during extraction, relatively high pressures are also applied (up to ca. 20 MPa). The rapid acceptation of PLE as a US Environmental Protection Agency (EPA) method [132] after its introduction in 1995 [133], probably contributed to its rapid acceptation as a relatively simple, fast, efficient, essentially analyte- and matrix-independent and rather green exhaustive extraction technique. Its main application areas at present are the environmental analysis [3,16] and the extraction of functional or added value components and food characterisation [134,135]. An overview of selected representative PLE approaches in use for the analysis of selected natural products, food and food-related matrices is presented in Table 3.

In agreement with that observed in the environmental field (see e.g. [16]), static PLE is preferred over the dynamic mode, probably to avoid analyte dilution and minimise solvent consumption. In most applications, an inert support is used for sample dispersion and packing of sorbents for in-cell purification of the PLE extracts is still rather the exception [137,138,144] than the rule. Practices like incorporating an in-cell washing step for interference removal before PLE of the target compounds [145] or sequential PLE for improved selectivity [138] are still scarce in the literature, and miniaturisation is up to now only possible with home-made instruments [138,150].

The potential of combining MSPD with PLE for selective-PLE have been demonstrated in several studies in general dealing with

Table 3
Selected representative application studies involving different PLE working modes and analytical strategies.

Matrix	Analyte	Dispersant	Extraction solvent	T (°C)/P (MPa)/t (min)[a]	Working mode/analytical strategy	Ref.
Poultry meat	Lipids	Hydromatrix	Chloroform/methanol (2:1, v/v)	120/20/10	Static – 2 cycles	[136]
Acid/base-hydrolyzed foods	Lipids	Diatomaceous earth + Prep CR Na^+/H^+ resin	*n*-Hexane	Acid: 100/10/5 Base: 110/10/15	Static – 1 cycle In-cell purification	[137]
Honey	Carbohydrates	Activated charcoal	Ethanol/water (1:99, v/v) Ethanol/water (50:50, v/v)	40/10/5 + 10	Static – 2 cycles Miniaturised Sequential extr. In-cell purification	[138]
Transgenic maize	Biomarkers	–	Water/methanol/*n*-hexane	100;175/10/20	Static – 1 cycle	[139]
Dunaliella salina	Carotenoids	Sea sand layered	Ethanol	160/10/17	Static – 1 cycle	[140]
Seeds and nuts	Tocopherols	Hydromatrix celite	Acetonitrile	50/10/10	Static – 2 cycle	[141]
Cereals	Tocotrienols and tocopherols	Hydromatrix celite	Matrix-dependent	50/10/5	Static – 1 cycle	[142]
Achillea monocephala	Essential oil	Glass wool	Water	150/6/30	Dynamic (2 mL/min) Off-line SPE	[143]
Grapes	Phenolic compounds	Sea sand	Methanol	100/4/30	Static – 3 cycles In-cell purification	[144]
Algae	Bioactive phenols	–	Acetone:*n*-hexane (1:1, v/v) Methanol:water (8:2, v/v)	130/13/15 130/13/20	Static – 3 cycles Static – 2 cycles Sequential in-cell pre-clean-up and extraction Off-line purification	[145]
Sambucus nigra	Flavonols and anthocyanins	Sea sand	Ethanol:water (80:20, v/v)	100/10/10	Static – 1 cycle Off-line SPE	[146]
Rubarb	Anthraquinones	Diatomaceous earth	Methanol	140/10/5	Static – 1 cycle	[147]
Origanum onites	Essential oils	Glass wool	Water	150/6/30	Dynamic (2 mL/min) Off-line SPE	[148]
Oak wood chips	(Semi-)volatile compounds	–	Dichloromethane	150/20/7	Static – 1 cycle	[149]
Oak wood chips	(Semi-)volatile compounds	–	Dichloromethane	60/10/20	Static – 2 cycles Miniaturised	[150]

[a] This time corresponds to the complete PLE process.

the determination of microcontaminants in very complex matrices, such as soils and sediments or fat-containing foods (see [3,16,134] and references therein). As an example, de la Cal et al. [151] demonstrated the efficiency of the combined use of MSPD (using alumina as solid support) with PLE for the selective and quantitative extraction, in a single step, of environmentally relevant polybrominated diphenylethers (PBDEs) from sediments. In a close related study, Westerbom et al. [152] proposed the use of silica modified with sulfuric acid for the efficient removal of matrix interferences in the analysis of polychlorinated biphenyls (PCBs) from sediments using dichloromethane at 100 °C as extraction solvent. This sorbent was also efficient for in-cell fat removal in the analysis of fat-containing foods of animal origin. Using such an approach and a home-made miniaturised PLE device, it was possible to obtain ready-to-analyse PCB extracts from fatty foodstuffs in only 15 min using only 3.5 mL of *n*-hexane. In this case, the extraction was carried out under relatively soft conditions (40 °C and 12 MPa) to minimise the co-extraction of interfering matrix components.

3.2.2. Microwave- and ultrasounds-assisted extraction

The efficiency of the extraction process can also be improved by the application of an auxiliary energy as in the case of MAE or ultrasonic extraction.

In principle, only samples or solvents containing dipolar materials or microwave absorbents are affected by microwaves. This explains the somehow limited use of microwave energy for the extraction of organic compounds as compared to other analyte types (e.g., metals). MAE can be conducted with open or closed vessels (focused microwave-assisted extraction, FMAE, and pressurised microwave-assisted extraction, PMAE, respectively). In the latter devices, up to 12 extraction vessels can be irradiated simultaneously. PMAE is quite similar to PLE, as the solvent is heated and pressurised in both systems. However, in PMAE, it is necessary to wait for the temperature to decrease before the vessels can be opened. Apart from increasing the total analysis time, this step can result in re-adsorption of the extracted analytes, something negligible in PLE as the solvent is removed from the extraction cell while still warm. For a more detailed discussion on the different modification carried out in MAE systems to circumvent some of the most pressing shortcomings of these basic configurations, the reader is addressed to texts of a more specific nature (e.g., [153] and references therein).

Probably the main advantage of MAE is its wide applicability for fast extraction of analytes, including some thermal labile compounds [2]. Application studies include the extraction of micropollutants from soils and sediments [154–156], polycyclic aromatic hydrocarbons (PAHs) from dust samples [157], pesticides from animal tissues [158], bioactive compounds from plants [159], polyphenols from grape seeds [160] or antibiotics from animal feed [161]. Although some examples of hyphenated MAE-based systems have been described [162–164], the difficulty to integrate MAE devices in a flow-system can be considered one of the main shortcomings of this technique. As an example of the complexity of such as set-ups, Fig. 10 shows the typical configuration used for dynamic MAE coupled on-line with a GC system for final instrumental determination of the tested analytes.

Sonication consists of the application of sound waves with frequencies above 20 Hz which travel through matter/liquid

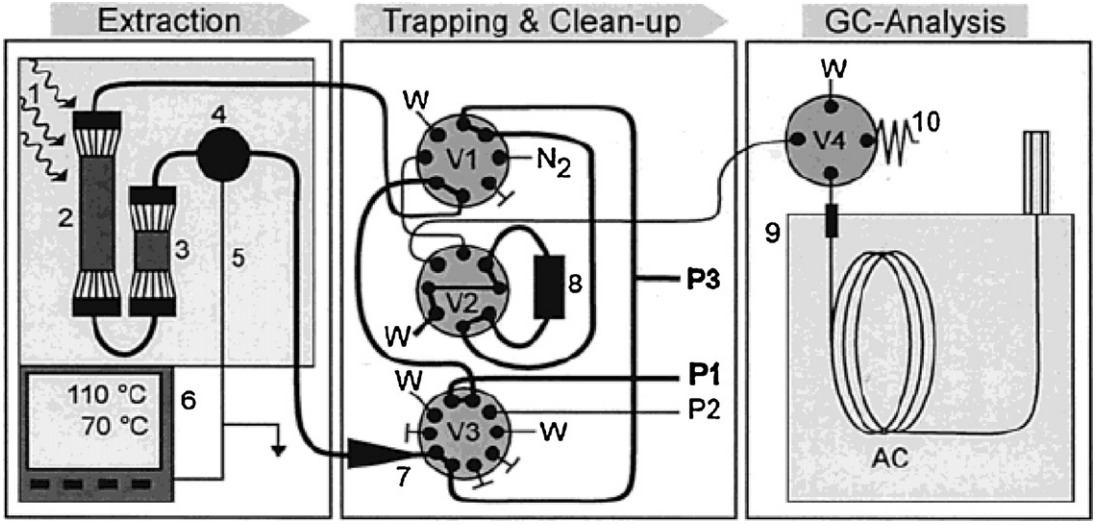

Fig. 10. Scheme of the DMAE-SPE-LVI-GC system: (1) microwave oven, (2) preheater, (3) extraction vessel, (4) mixing tee, (5) thermocouple, (6) temperature regulator, (7) restrictor, (8) SPE cartridge, (9) PTV-GC-NPD, and (10) fused-silica leak [163].

producing negative pressure and bubbles or cavities. When a bubble can no longer efficiently absorb the energy from the ultrasound, it implodes [1]. The whole process is named "cavitation" and creates microenvironments with high temperatures and high pressures that speed the removal of analytes from sample matrices.

Despite its many positive features, the use of ultrasounds for analytical purposes started only some 20 years ago. Nevertheless, some applications have already demonstrated the potential of sonication for fast, relatively inexpensive and quantitative extraction of several types of analytes, ranging from metals to different classes of organic compounds, from a variety of matrices [1,165–167].

The devices most frequently used for ultrasound-assisted extraction (USE) are ultrasounds baths, sonoreactors and probe systems. The baths are more widely used, but have two disadvantages that adversely affect experimental precision: a lack of uniformity of the distribution of ultrasound energy (i.e., in practice, only a small fraction of the total liquid volume in the immediate vicinity of the source will experience cavitation) and a decline of power over time. On the contrary, probes focus their energy on a localized sample zone and so provide more efficient cavitation in the liquid. However, cooling of the sonication vessel is required due to the large amount of heat generated, volatile analytes can be lost due to the high temperatures and tip erosion occurs over time as a result of cavitation [1]. In general, the extraction times decrease from baths to sonoreactor, and from this to probes; and in all three cases subsequent clean-up of the obtained extracts is typically carried out off-line. Examples involving dynamic extraction (DUSE) with on-line purification are still scarce in the literature. In open systems, the sample is packed in a refillable column, which is immersed in an ultrasonic bath, and the extraction solvent flows continuously through the sample. Using this set-up on-line coupled to LVI-GC via a PTV, Sanchez et al. [168] quantitatively extracted organophosphate esters collected from air on 25 mm binder-free A/E borosilicate glass fiber filters. The extraction was completed in 3 min with only 600 μL of hexane:methyl tertbutyl ether (7:3, v/v). In closed system, the extraction column containing the sample is filled with an appropriate volume of extraction solvent, immersed in a water bath and sonicated with an ultrasonic probe. The solvent can be moved back and forward within the column at pre-set intervals to avoid the compaction of the sample. After a pre-selected extraction time, the eluate is either collected in a vial or on-line transferred to the next step of the analytical procedure [169].

Interestingly, the ultrasound energy has recently been used to speed up other extraction or purification processes, such as SPE [170] or MSPD [171]. The first approach was used by Albero et al. to increase the rapidity and efficiency of SPE of pesticides from juice. In the second one, the MSPD mixture, packed in a close SPE cartridge, was wetted with the selected extraction solvent and placed in a sonoreactor for a pre-selected time. Then, the extracted analytes were eluted from the column and directly subjected to instrumental analysis. The feasibility of this so-called ultrasonic-assisted matrix solid-phase dispersion (UA-MSPD) was illustrated for the analysis of selected triazines and organophosphorous pesticides from fruits contaminated at levels similar to the MRL set in EU legislations. Complete sample preparation was accomplished in only 1 min and involved only 100 mg of fruit peel, a similar amount of dispersant sorbent and a few mL of organic solvent.

4. Conclusions

It is often said that sample preparation is the bottleneck of most analytical procedures. The many efforts carried out during the last two to three decades to improve this situation have resulted in the development of new analytical approaches based on previous or completely novel concepts. Some of these new techniques have contributed to solve some of the most pressing shortcoming of conventional sample treatment procedures, which are characterised by long analytical times, much manual manipulation of the extracts, large consumption of sample and reagents, exposition of the analyst to hazardous products and generation of large amounts of wastes. Today, on-line coupling (with or without automation) is a recognized feature in many areas of application which deal with gases or volatile analytes, and with a wide variety of analytes of divergent polarity in liquid samples (water, urine and plasma, soft drinks, and spirits). The development of procedures similar to these for semi-solid and solid samples has been more limited, probably because of the difficulty of the initial extraction step, and large-scale (off-line) approaches are mainly used. However, in the last 15 years, some interesting advances have also been done in this field and a group of powerful, versatile, greener and in some cases already widely accepted techniques (with MSPD and PLE as prominent examples) are now available. Although the attempts for on-line coupling of these techniques with the subsequent steps of the analytical procedure are still scarce, the preliminary results obtained in this field have demonstrated that, similarly to that observed for gaseous and

liquid samples, miniaturisation of the techniques and approaches is probably a key aspect when attempting (at least partial) integration of the systems as a way to improve the analytical performance and throughput. However, to achieve a level of development and maturity similar to that shown at present for other solvent or sorbent-based techniques, more work is still demanded from both academia and, especially, companies, who should support and promote the development of appropriate analytical instrumentation.

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