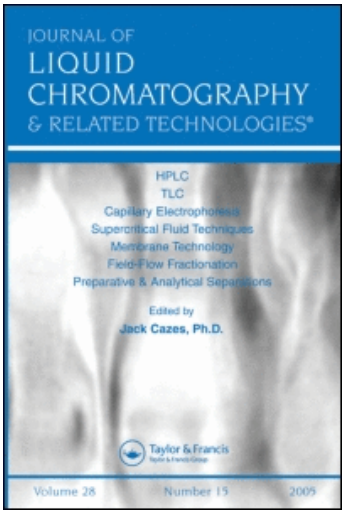

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SAMPLE PREPARATION FOR TRACE ANALYSIS BY CHROMATOGRAPHIC METHODS

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□ *The determination of trace analytes in complex natural matrices often requires extensive sample extraction and preparation prior to chromatographic analysis. Correct sample preparation can reduce analysis time, sources of error, enhance sensitivity, and enable unequivocal identification, confirmation, and quantification. This overview considers general aspects on sample preparation techniques for trace analysis in various matrices. The discussed extraction/enrichment techniques cover classical methods, such as Soxhlet and liquid-liquid extractions along with more recently developed techniques like pressurized liquid extraction, liquid phase microextraction (LPME), accelerated microwave extraction, and ultrasound-assisted extraction. This overview also deals with more selective methodologies, such as solid phase extraction (SPE), solid phase microextraction (SPME), and stir bar sorptive extraction (SBSE). The adopted approach considers the equilibriums involved in each technique. The applicability of each technique in environmental, food, biological, and pharmaceutical analyses is discussed, particularly for the determination of trace organic compounds by chromatographic methods.*

Keywords chromatographic analysis, enrichment techniques, gas-liquid, gas-solid equilibriums, liquid-liquid, liquid-solid, sample preparation

INTRODUCTION

It has long been established that knowledge on complex chemical systems in matrices of interest for the human beings, in various ways, is critically dependent on chromatographic methods. Sensitive and robust analytical methods, among which chromatography is quoted by far as the most important, have been widely used during the past decades to investi-

Address correspondence to Cecilia Arsene, Department of Chemistry, Faculty of Chemistry, Laboratory of Analytical Chemistry, "Al. I. Cuza" University of Iasi, Carol I 11, 700506 Iasi, Romania. E-mail: carsene@uaic.ro

gate and identify various chemical compounds characterized by varying degrees of structural complexity.

Modern analysis involves undertaking each single step of a complete analytical diagram flow, beginning with the definition and outline of the problem and ending with a detailed critical evaluation of the relevant analytical data which allows the presentation of the analytical result. Sample preparation and the use of adequate analytical methods represent the bridge between the two aforementioned steps, which will be largely dependent upon analyst experience.

In practical work, analysis of trace chemicals entails more than the mere qualitative or quantitative detection and identification of a particular element or chemical compound. It involves knowledge of the origin and structure of the sample matrix, and also the analyst's insight into analogous problems from other disciplines to assure the plausibility of the questions raised and to critically evaluate and interpret the results. It is suggested that these preliminary observations are essential in trace analysis, where an important focus is in sample preparation. Nevertheless, it is admitted that tools, equipment, and methodological principles are common to both general chemical analysis and modern trace analysis.[1]

The concentration levels of target analytes found in environmental, biological, food, and drugs samples are generally too low to allow a direct injection into a chromatographic system. Changing solvent, temperature, pressure, phases, or volumes are among the main tools used by analysts in order to solve a complex chromatographic problem. Most of the sample preparation techniques rely on analytical steps including trapping of the analytes of interest on various media, desorption and analysis (mainly by chromatography). Poor sensitivity, the major problem in these procedures, is presently overcome by including on-line combination of extraction with liquid chromatography and injection of large volumes into the analytical system (i.e., gas chromatography).[2]

The main goal of sample pretreatment is to make complex samples suitable for chromatographic analysis.[3] This prerequisite is necessary to reach detectable concentration of the target analyte and to isolate the analytes from very complex matrices.

Quite often, the sample preparation in chromatographic methods is representing a tedious, time-consuming, and error-prone step of an analytical procedure. Therefore, it is generally regarded as the rate-limiting step in chemical analysis. It has been suggested that a large part of the time typically required to perform analytical tasks is spent on sample preparation.[4] Indeed, sample pretreatment is frequently performed by off-line methods (e.g., liquid-liquid extraction and solid-phase extraction). These procedures are usually performed manually, they are laborious and time-consuming and sometimes lack precision and accuracy.

THE STATE-OF-THE-ART IN CHROMATOGRAPHIC INVESTIGATIONS TOWARD SAMPLE PREPARATION: A GENERAL APPROACH

At the beginning of the chromatographic technique, insufficient detection limits, and the occurrence of many problems with sample preparation and separation, preventing the analysis of real samples, were often acknowledged as major challenging aspects that chemists were facing in their experimental work.[5] Recent progress in instrumental analytical chemistry has resulted in the availability of methods that allow monitoring of various chemicals at parts per trillion (ppt) and even parts per quadrillion (ppq) range.

A number of important papers of fundamental and comprehensive review brought the importance of choosing and using suitable analytical techniques for the determination of trace residues and contaminants in complex matrices to the attention of the scientific community. Presently, a topic of great concern and interest is the analyses of the potential genotoxic impurities (PGIs) in pharmaceutical products. PGIs have received increased consideration over the last years.[6] A threshold of toxicological concern (TTC) value of 1.5 μg day^{-1} has been developed as an acceptable risk associated with the intake of a genotoxic impurity.[7] Analyzing the PGIs, even at low ppm levels in active pharmaceutical ingredients (APIs), is a challenging task, which presently can be performed through the use of state-of-the-art technology. Currently, quantifying chemicals at such low levels does not seem feasible in order to routinely control the level of the impurities that might reside in active pharmaceutical products and, despite the demand for sensitivity to detect trace concentrations, matrix interference and selectivity will represent important issues to overcome.[6] Modern hyphenated techniques, involving static headspace sampling (SHS) coupled with capillary gas chromatography interfaced to mass spectrometry (GC-MS) are presently available for the analysis of halides and haloalkenes,[8] while *in situ* derivatization by SHS-GC-MS is more suitable for the analysis of aryl- and alkyl sulfonates.[9] Vanhoenacker et al. in 2009 proposed a sample preparation method where liquid chromatography (LC) is preferred for the analysis of less volatile solutes.[6]

Presently, a number of reviews and original papers is available on the state-of-the-art chromatographic methods for residue analysis of pharmaceuticals in samples of environmental concern,[10] for trace residues and contaminants in foods and drinks,[11–13] for mycotoxins in biological tissues[14], or for surfactants (e.g., alkylbenzene sulfonates, ethoxylated nonionic surfactants, metabolites) in river water or wastewater.[15,16] Major modern sample preparation techniques for the extraction and analysis of medicinal plants were reviewed by Huie in 2002, and the author concludes

that the solid-phase microextraction represents the most suitable alternative for the sampling of volatile compounds before chromatographic analysis.[17] Baltussen et al., in an excellent review regarding sorptive sample preparation, concluded that this is a valuable strategy to overcome the limitations of the adsorptive sampling. The technique is used in combination with thermal desorption for the analysis of very apolar analytes (i.e., alkanes, alkenes, and aromatics).[2]

As far as sample preparation is concerned, the hyphenation of various techniques has been gaining importance over the past decades. Sample pre-concentration and clean-up methods hyphenated with core analytical techniques are acknowledged as powerful tools to accomplish the task of low-level detection.[18] Hyphenated (coupled or hybrid) techniques, coupling chromatographic separation with sensitive and specific detectors (usually mass spectrometry), has recently become one of the most powerful instrumental tools in speciation analysis and the characterization of complex samples.

Liquid or gas chromatographic methods coupled with mass spectrometric detection play an increasingly important role in environmental analysis, especially in the aquatic environment and in water treatment.[19,20] Hydrophilic interaction chromatography (HILIC) hyphenated with mass-spectrometry (MS) is a potentially powerful technique in the quantitative analysis of drugs and drug metabolites.[21] High-performance liquid chromatography stability-indicating methods are particularly attractive for the determination of active substances (e.g., ascorbic acid) and for the quantification of potentially occurring degradates in pharmaceutical/cosmetic preparations, developed as oil-in-water emulsion and aqueous gel.[22] Such a method presents convenience, rapidity, and the ability to separate substances quantitatively without pre-derivatization.

There is also an important number of reports which refer to fast, simple, sensitive, and efficient sample preparation methods prior to analytical detection of a wide range of persistent organochlorine pollutants,[23] polychlorinated biphenyls in soils,[24] iodixanol used as a contrasting agent,[25] sodium azide used as a preservative,[26] pharmaceuticals, drugs, anesthetics, and metabolites,[27–36] and even adjuvants (epichlorohydrin) in paper and pharmaceutical industries.[37] Presently, also in the enantioselective analysis of various drugs marketed as racemic mixtures, tedious sample preparation methods turned towards more rapid and feasible procedures.[38]

It is generally agreed that the works that are mainly serum/plasma related are especially important for assessment studies of health issues related to human exposure.[23] However, matrices of physiological concern, such as plasma, serum, and biological tissues, were previously assigned as being particularly complex, with numerous sample preparation problems.[27] Major problems that should be addressed in the sample

preparation step are the presence of interference masking the analytes of interest, of non-analytes progressively reducing the performance of the analytical column, and the variability between the samples induced by the multitude of the non-analytes.

Presently, limits of the chromatographic methods to simultaneously detect several water-soluble vitamins in complex matrices require identification and use of separate assay methods. Sample preparation, sensitivity of the detection method that is used, and equipment costs are among the main problems limiting the use of chromatographic methods in routine analysis of, for example, ascorbic acid. Therefore, it is suggested that chromatographic methods be replaced by flow injection analysis (FIA) based on spectrophotometric or electroanalytical detectors, which is a more suitable tool to solve analytical problems characterized by time-consuming procedures of extraction, reaction, and analysis, or when only one analyte has to be determined in a large number of samples.[39] However, in 2003, Iwase supplied excellent preparative aspects for the routine chromatographic analysis of ascorbic acid in food.[40] Vinci et al., in 1995, claimed that, by improving the chromatographic conditions and the sample pretreatment operations, it is possible to optimize and make easier the overall procedure of analysis of ascorbic acid in fruits with high nutritional value, which contain generally high levels of hydrosoluble vitamins.[41]

In samples of environmental concern, the methods used to isolate trace volatiles for gas chromatographic analysis may have profound effects on the resultant chromatograms.[42] *Per se* injection was the usual method used in the past for the analysis of samples containing low-boiling petroleum fractions or essential oils. Additional problems may occur with samples containing large amounts of water, alcohol, or nonvolatile materials (including most food products), or samples containing volatile compounds as dilute vapor systems (e.g., air or headspace gases).

In some cases, the development of appropriate preparation steps is also a crucial prerequisite for studies intended at understanding the separation process at the molecular level, where both experimental observation and theory must be put forth.[43–47]

High sensitivity with no column overloading and adequate resolution is challenging tasks that can be solved nowadays. On-line on-column derivatization at controlled temperature is regarded as a useful method for the analysis of an active aldehyde,[48] while on-line column-switching devices combined with advanced separation media technologies is regarded as a suitable technique for the analysis of complex matrices (e.g., mixtures of enantiomers specific for various cardiovascular drugs).[49] Presently, ultra high pressure liquid chromatography is largely used for fast enantiomeric separation of chiral molecules,[50,51] the absolute configuration of the

enantiomeric analytes being assessed with the help of the vibrational circular dichroism (VCD). VCD is a technique capable of solving problems of absolute stereochemistry[52] under specific experimental conditions.[53]

Lowering the temperature at which the separation occurs is a suitable alternative to studying active compounds or unstable molecules. Extensive in-column cyclization of an analyte, occurring at room temperature, can be significantly diminished when working at sub-ambient temperature.[54]

THE CHOICE OF A SUITABLE SORBENT PHASE

Various materials are successfully used for the selective adsorption of the analytes of interest from complex matrices, although undesired effects (incomplete desorption, artifact formation) may also occur.[2] The sorbent materials can be adopted as stationary phases in chromatography or employed in the step of sample preparation for extraction and clean-up purposes. Many research groups have attempted to prepare suitable sorbents for the separation of various compounds. Production of novel capillary GC stationary phases based on persubstituted cyclodextrins have attracted a great deal of attention during the past decades, especially for their potential application in the separation of chiral silicon compounds.[55]

Fundamental studies on intermolecular interactions influencing solute retention on novel carbon surfaces prepared by vapor deposition on porous zirconia microspheres proves that these carbon sorbents may considerably improve the chromatographic separation.[56]

The introduction of polar embedded-phases, containing polar moieties within an alkyl chain, involves changing the chemistry of the stationary phase itself in order to set-up parameters to improve the selectivity or reproducibility. Modeling studies have proved that reduced peak tailing can be obtained with the use of stationary phases with embedded polar groups, compared with conventional alkylsilane phases.[57]

Strong cation-exchange supports are suitable extractors for the determination of Triton-X 100, a surfactant used in reaction mixtures in order to increase the solubility of various compounds and to provide homogeneous reaction environments. For instance, it is used as a surfactant in the presence of quinoline derivatives from the leukotriene D_4 class, which is a therapeutic agent with a potentially important role in the etiology of various diseases. Development of flow injection methods with on-line solid-phase extraction offered the most suitable solutions to solve practical aspects related to the instrumental maintenance, which also enabled the chromatographic columns to operate for longer times. The method has also solved a complex problem regarding the analysis of a surfactant that appears as a mixture of various oligomers, with important implications in

its quantification. Flow injection analysis with on-line solid phase extraction represent a simple, rapid, and accurate method for Triton-X 100 determination.[58,59]

On a C18 hybrid stationary phase, using pure water as a mobile phase at temperature above 100°C, a temperature range where the solvation properties of pressurized hot water changes, it is possible to separate complex mixture of organic constituents in a short time period.[60,61] Under such conditions, it is possible to separate at least 12 anilines in less than 10 min,[61] to be compared with a total analysis time of about 80 min as reported by Gennaro et al.[62]

METHODS OF ANALYTE ISOLATION AND CONCENTRATION/ ENRICHMENT TECHNIQUES

The choice of the suitable extraction/enrichment techniques for the recovery of trace chemicals from various samples (biological, drugs, environmental, food, and drinks) must take into account the sensitivity, selectivity, and separation capabilities of the selected analytical method, the complexity of the sample, and, last but not least, the chemical and physical characteristics of the analytes.[15]

In the last few years, on-line dialysis has been successfully applied to the LC determination of several drugs in biological fluids and especially in plasma. The sample preparation is normally carried out using the ASTED (Automated Sequential Trace Enrichment of Dialysates) system connected on-line with an LC system. Chiap et al. described such an automated procedure for the chromatographic determination of various chemicals (i.e., sotalol and human anesthetics) in human plasma. The method involves on-line dialysis, enrichment of the dialysate on a precolumn that has been prepacked with a strong cation-exchange material, and subsequent LC analysis using UV detection. The studies described are among the first experiments where a combination of dialysis with the enrichment of the dialysate on a cation-exchange sorbent was used.[33,34]

However, prior to the chromatographic analysis, complex samples may require multiple preparation techniques. For biological matrices, the complex of techniques may consist of deproteinization of the plasma samples, liquid–liquid extraction after alkalinization followed by back extraction in an acidic medium, as well as solid phase extraction on disposable cartridges after deproteinization or alkalinization. These are off-line procedures that are often performed manually and, therefore, are laborious and time-consuming. Under these circumstances, when the number of samples to be analyzed is particularly large, the automation of sample preparation often becomes a necessity. On-line automated LC procedures based on a

column-switching technique or on-line sample preparation involving dialysis and trace enrichment on cation-exchange pre-columns have been recently developed.[33,34] The trace enrichment system is incorporated to overcome the dilution of the sample caused by dialysis and to improve method selectivity.

In 2007, in an excellent review, Ridgway et al. treated many aspects of sample preparation.[12] They referred to the determination of trace residues and contaminants in complex matrices, such as food, which often requires extensive sample extraction and preparation prior to instrumental analysis. The idea was to offer analysts with an excellent background in selecting suitable extraction and concentration methods, which should move toward more environmentally friendly techniques, using less solvent and smaller sample sizes. In 2009, Nerin et al. are critically reviewing all recent developments in solventless techniques for the extraction of analytes in different areas.[63]

TECHNIQUES AVAILABLE TO INCREASE SELECTIVITY AND SENSITIVITY

A wide range of sample preparation techniques are presently available for the analysis of the three states of matter (gas, liquid, and solid). Modern sample preparation techniques were developed and they gained more importance over conventional methods due to their major advantages (i.e., reduction in organic solvent consumption, improved clean-up procedures and concentration steps before chromatographic analysis, increases in extraction efficiency and selectivity). In this context, analysts' skills are completed by a full understanding of the theoretical aspects of equilibriums in liquid-liquid, liquid-solid, liquid-gas, and gas-solid systems.

In the present paper, the sample preparation techniques for trace analysis by chromatographic methods have been classified based on two equilibrium types: liquid-liquid or liquid-solid equilibriums, and gas-liquid or gas-solid equilibriums. This review considers most of the aspects of sample preparation for trace analysis by chromatographic methods. It covers general extraction techniques, such as liquid-liquid extraction; Soxhlet and pressurized liquid extraction; microextraction techniques, such as liquid phase microextraction (LPME); and more selective techniques, such as solid phase extraction (SPE); solid phase microextraction (SPME); and stir bar sorptive extraction (SBSE), including their most recent developments and applications.

The theory of the extraction process is not covered in this review as this aspect is the subject of several books that treat comprehensive theoretical and practical aspects concerning sample preparation techniques in different research areas.[64–66]

Derivatization

Derivatization is a chemically driven process usually incorporated into an analytical method to facilitate chromatographic separation to increase selectivity and to improve the limit of detection. Although numerous methods have been reported and several books cover the technique, only a few reactions are widely used in routine analysis.[67,68]

Most derivatization methods for gas chromatography involve esterification or etherification. For example, an analytical method has been developed to identify compounds containing one or more carbonyl, carboxy, and hydroxy functional groups in atmospheric samples. In the method, –C=O groups are derivatized using O-(2, 3, 4, 5, 6- pentafluorobenzyl) hydroxy amine (PFBHA), and −COOH and −OH groups are derivatized using the silylation reagent N,O-bis(trimethylsilyl)- trifluoroacetamide (BSTFA).[69–72] Derivatization can also be performed on fiber/coatings before, during, or after sorptive extractions.[73]

Derivatizations for HPLC are designed mainly to improve the limit of detection, permitting the use of highly sensitive or selective detectors inapplicable to the analytes themselves. Enhanced absorption of UV-visible light is achieved by the introduction of chromophoric groups. Analytes can also be rendered fluorescent by the introduction of fluorophoric groups.

Carboxylic acids can be transformed into esters that absorb UV or visible light by reacting with 1-naphthyldiazomethane[74] or bromophenacyl bromides.[75] α-Keto acids (e.g., glycolic, glyoxylic acids) are detectable with UV light after derivatization with 2,4-dinitrophenylhydrazones.[76] Fluorescent compounds are obtained by reacting carboxylic acids with 4-bromomethyl-7-methoxycoumarin[77] or 4-hydroxymethyl-7-methoxycoumarin.[78] Analytes containing hydroxyl groups, such as phenols, glycols, and alcohols, can be converted with 3,5-dinitrobenzoyl chloride into compounds that absorb UV or visible light.[79] Fluorescent derivatives can be obtained with 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin.[80] Derivatizations for HPLC purposes are accomplished either off-line or on-line. An on-line process may involve either precolumn or postcolumn reaction, depending on the analyte under consideration and the adopted instrumentation. In the case of pre-column derivatization, it is essential to check its compatibility with the separation process.

Separation and Enrichment Techniques Driven by Liquid-Liquid or Liquid-Solid Equilibriums

Liquid-Liquid Extraction

Liquid-liquid extraction is one of the most common methods of extraction, particularly for organic compounds from aqueous matrices. It

is a simple, manual, and off-line extraction procedure, used almost exclusively in the 1980s. It involves extraction of analytes in solution or liquid samples by direct partitioning with an immiscible solvent. Repeated extractions might ensure the complete partitioning of the interest analyte into the required phase. Clean-up or analyte enrichment/concentration steps, prior to instrumental analysis, may help for trace level analysis and improve the selectivity of the whole method.[81,82]

The major disadvantage of liquid-liquid extraction is the need for large volumes of organic solvents; the formation of emulsions may represent a relatively frequent problem.[15] In liquid-liquid extraction, there is a tendency for compounds to adsorb on all phase boundaries, which can lead to the formation of emulsions and prevent a complete phase separation. In some cases, to avoid emulsions, salt may be added and centrifugation or freezing can be used if necessary.[12,83]

The demixing/microextraction approach is very appropriate for GC-MS analysis, as it is a procedure that avoids the imprecise solvent evaporation steps. It can be applied to water-ethanol mixtures (e.g., wine) and consists of the separation between water and ethanol, achieved by addition of salts, followed by microextraction of the analytes from the ethanolic phase. Extraction is performed at laboratory temperature, ultra high purity solvents are not required, and the final extract can be cleaned enough if the extraction conditions are correctly chosen.[11]

Within the liquid-liquid extraction process, the decisive parameter is the distribution coefficient for the analyte between the particular phases involved. If the distribution coefficient is sufficiently large, the simplest approach to liquid-liquid extraction is shaking the sample with an appropriate amount of an organic solvent. The distribution coefficient can be pH dependent, dividing the sample into strongly or weakly acidic, neutral, or basic fractions.[84]

With smaller distribution coefficients or large sample volumes, continuous extraction or countercurrent extraction is required to achieve a complete separation. The apparatus for continuous extraction causes a liquid immiscible with the sample solution to circulate continuously through the sample.[85] Extracted analytes are concentrated by distillation at appropriate times between individual extraction cycles.

More recently, classical liquid-liquid extractions have been replaced by modern, efficient and versatile microextraction techniques. The time needed to reach equilibrium and the volume of solvent needed for the quantitative recovery of analytes switch the preference toward more modern methods. They are more and more frequently adopted both in organic synthesis laboratories and for the separations of metal complexes, metal chelates, and/or ion-pairing reagents.[65]

Although old in fashion, a variant of liquid-liquid extraction takes advantage of a liquid phase immobilized on a solid sorbent such as

kieselguhr, Celite, Chromosorb W, or Chromosorb P.[86] In this method, the immobilized phase may be either aqueous or non-aqueous.

An "in-line" liquid-liquid extraction (LLE) system is created in hydrophilic interaction chromatography (HILIC), where the mobile phase forms a water-rich layer on the surface of the highly polar stationary phase. The mechanism involves distribution of the analytes between the water-rich stationary layer and the mobile phase with mostly organic content. The analytes possessing higher polarity will have a higher affinity to the stationary aqueous layer than the analytes possessing weaker polarity. As HILIC requires a high-organic and low-aqueous mobile phase, which are favorable conditions for MS in terms of sensitivity, HILIC appears to be a preliminary preparative step in MS analysis.[21] A technical and cost effective method for a therapeutic drug monitoring program of ribavirin (a synthetic purine analogue of guanosine, used in the standard treatment of chronic hepatitis C virus) proposes hyphenation of a liquid/liquid extraction method coupled with HPLC-UV measurements.[87]

Soxhlet Extraction

Soxhlet extraction, a liquid-solid equilibrium technique, has application in sample preparation prior to chromatographic analysis. It is basically a leaching technique based on two processes: 1) reflux boiling of a solvent, and 2) a siphon procedure. This technique has already been reviewed.[88,89] Recent developments have included the use of focused microwave-assisted extraction; ultrasonic extraction has been used to improve extraction efficiencies.[90,91]

The large volume of solvent that is needed for the sample extraction, the extra step required to concentrate the sample after solvent evaporation, the lack of thermal stability, the volatility of some sample analytes, and the interference from contaminants in the extraction thimbles (requiring a blank extraction prior to sample extraction) limit the application of this technique. Although exhaustive, the Soxhlet technique is not selective and further clean-up is necessary. Due to the temperatures involved, Soxhlet extraction can degrade thermally labile compounds.[89] Most applications of Soxhlet extraction are for environmental samples, such as soil, but it has been used for the analysis of food followed by further clean-up.[88,92,93]

Automated Soxhlet extraction systems are available, which claim to greatly reduce extraction times and perform boiling, rinsing, and solvent recovery automatically. Up to 6 samples can be extracted simultaneously and lower volumes of solvent can be used.[88]

Ultrasound-Assisted Extraction (USE)

Ultrasound-assisted extraction (USE) is among the easiest and most reliable of the wide range of available extraction techniques.[94] Ultrasound

assistance is a growing trend in analytical chemistry.[95] The technique is performed statically and utilizes energy in the form of acoustic sound waves to accelerate mass transport from a solid sample immersed in a solvent. The extraction setup is uncomplicated. Normally, an ultrasonic bath filled with water and a number of extraction vessels, together with a relatively strong solvent or mixture with appropriate properties for the targeted analytes and matrix, can be selected to obtain maximum extraction efficiency and required selectivity.[96] This is a fast technique but efficiency is not as high as with other techniques. Low concentrations of analytes in samples require multiple extractions. Several extractions can be performed simultaneously. The technique is relatively inexpensive compared to most modern extraction methods, because no specialized laboratory equipment is required. One important disadvantage of ultrasound-assisted extraction is that it is not suitable for volatile analytes.

Herrera and Luque De Castro in 2005 used an ultrasound-assisted extraction technique followed by HPLC for the analysis of phenolic compounds from strawberries,[97] and Rezic et al., the same year, used ultrasound-assisted extraction and thin-layer chromatography for the determination of pesticides in honey.[98] Kimbaris et al. performed a comparison of distillation and ultrasound-assisted extraction methods for the isolation of aroma compounds from garlic.[99] Other applications of the USE technique include extraction of polycyclic aromatic hydrocarbons (PAHs) from lichen samples,[100] determination of polyphenols in tobacco,[101] determination of butyltin and phenyltin species in sediments,[102] determination of organophosphorus pesticides in sludge,[103] and determination of triazine herbicide residues in horticultural products.[104] However, as both selectivity and sample enrichment capabilities are limited, further clean-up and/or concentration steps are usually required for the determination of trace analytes in several matrices.[104,105]

Microwave-Assisted Extraction (MAE)

In recent years, microwave-assisted extraction (MAE) has attracted growing attention as it allows rapid extraction of solutes from solid matrices, with extraction efficiency comparable to that of the classical techniques.[106,107] Accelerated dissolution kinetics is produced in MAE as a consequence of the rapid heating processes that occur when a microwave field is applied to a sample. Microwave-assisted extraction gained enlarged attention due to its applicability to a wide range of sample types, and because the selectivity can be easily manipulated by altering solvent polarities.[108] There are studies suggesting that MAE affords a lower solvent consumption than pressurized liquid extraction (PLE, *vide infra*).[109]

An overview of the different microwave-based devices used for solid sample pretreatment has been published in 2003.[110] The authors described multi-mode and focused microwave devices, as well as closed and open systems. Special open systems, such as a microwave-ultrasound combined reactor, a focused microwave-assisted Soxhlet extractor, a microwave-assisted dryer, and a microwave-assisted distiller were discussed. Finally, there are brief comments on microwave-assisted robotic methods, and closed and open microwave systems are compared.

Because of its applicability to solid, semi-solid, and liquid matrices, microwave-assisted (MAE) extraction has emerged as a powerful sample preparation technique. It is only applicable to thermally stable compounds due to the increase in temperature during extraction. Although MAE can be used also for leaching purposes, nowadays, its power in sample solubilization is mostly used for samples dissolution/digestion.

The main applications of MAE are as an alternative to Soxhlet extraction as good extraction efficiencies can be achieved using less solvent and shorter extraction times.[111] Most publications to date have been for environmental applications, although Hermo et al. present the comparison between two analytical methods used for the determination of quinolones in pig muscle.[112] The procedures involve the extraction of the quinolones from the tissues by traditional extraction and using microwave assisted extraction (MAE), a step for clean-up and preconcentration of the analytes by solid phase extraction, and subsequent liquid chromatographic separation with UV absorbance detection. In that study,[112] microwave-assisted extraction (MAE) has proven to be an alternative to classical extraction because less interfering substances were observed and cleaner extracts were obtained. As with Soxhlet extraction, further extraction or clean-up steps such as solid phase extraction (SPE) are generally required, particularly for the determination of trace contaminants.[113]

Accelerated Solvent Extraction (ASE)

Accelerated solvent extraction (ASE), sometimes referred to as pressurized liquid extraction (PLE) or pressurized fluid extraction (PFE), may be used for solid and semi-solid samples. The elevated temperatures and pressures used in these techniques are causing reduction in dipole interactions and hydrogen bonds, increasing the surface wetting. ASE has the advantage that water may also be used as solvent, if it is below the critical point.

Often, due to a large number of samples that need to be analyzed, methods to speed up the extraction process have been widely examined. ASE involves extraction with liquid solvents but at elevated temperatures and pressures. In ASE, the sample is heated in the presence of an

extraction solution at high pressures, up to 2000 psi. Like the closed-vessel microwave approach, this technique utilizes the fact that liquids at elevated pressure can be heated to temperatures above their respective boiling points without transition to the gaseous phase. Several other names have been used for this technique, including pressurized fluid extraction PFE), high-pressure solvent extraction (HPSE), high-pressure, high temperature solvent extraction (HPHTSE), pressurized hot solvent extraction (PHSE), and subcritical solvent extraction (SSE). Carabias-Martinez et al. reviewed the distinct advantages of this technique exploited in several areas, including biology and the pharmaceutical and food industries.[114] A relatively new variant of ASE switches the usual procedure to superheated water extraction when water is used as a solvent. A review of the technique, including several applications, was given recently by Smith.[115]

ASE provides faster extractions than conventional Soxhlet techniques, because of the accelerated desorption of analytes from the matrix and the more rapid kinetic processes for dissolution.[116,117] In the case of most organic solvents, diffusion rates increase exponentially with temperature. Due to the lower viscosity and higher diffusivity of the solvent, mass transfer into the extraction solvent is faster. The higher temperatures also make it easier for the solvent to overcome intermolecular interactions of the analyte and matrix effects.

The nature of the extraction procedure in ASE is both static and dynamic. The procedures may involve a certain number of extraction cycle(s), the extraction cell being flushed with a pre-determined volume of fresh solvent and then purged with nitrogen gas (N_2) in order to recover all of the extraction solvent and analyte.

In specific applications, further clean-up is usually required for some target analytes. Sometimes, the clean-up step can be done *in situ*, by adding sorbent materials or a desiccant (e.g., sodium sulfate) directly to the extraction cell. When the *in situ* clean-up procedure is not strictly required, after performing ASE, it is possible to use a typical sorbent to produce the cleanest extracts for target samples from the initial extract.[118] Other clean-up steps coupled with the ASE technique and their details can be found in the literature.[84,91,119–121]

Preliminary ASE, with non-polar solvents to eliminate the hydrophobic compounds prior to the extraction of the analytes of interest, represents an alternative approach. There are some situations when elevated temperatures and pressures are not enough to dissolve analytes from a complex matrix. In such a case, modifiers (e.g., sodium dodecyl sulfate) can be added to the extraction solvent.[122]

The application of ASE as a sample preparation technique for the analysis of matrix components in food and biological samples was already reviewed in 2005.[114] Since then, many other applications of this

technique for the determination of organic analytes from different matrices have been published.[123–127]

Subcritical Water Extraction (SWE)

In the last few years there has been an interest in the use of water as the solvent for pressurized liquid extraction as this can reduce or eliminate the use of organic solvents.[128] This technique usually adopts water in the condensed phase between 100°C and the critical point, and it is generally referred to as superheated water extraction (SHWE). It has also been called subcritical water extraction (SWE), hot water extraction (HWE), pressurized hot water extraction (PHWE), or high temperature water extraction (HTWE). SHWE is cleaner, faster, cheaper, and more environmentally friendly than conventional methods.

Water as a solvent is unique due to its high level of hydrogen-bonding, giving it a high boiling point and high dielectric constant and polarity. As the temperature of water is increased (under pressure), the polarity decreases and, therefore, extraction becomes more selective. At 100–374°C it can act as a medium/non-polar solvent.[129] The useful temperatures and pressures of water for SWE are lower than the critical point, in contrast to super-critical fluid extraction (SFE) with carbon dioxide. A review of the SWE technique, including several applications was given by Smith in 2006[115] and more recently in 2008.[129] Most applications to date are for solid samples, such as soil, and include the determination of selected polycyclic aromatic hydrocarbons (PAHs), polychlorobiphenyls (PCBs), and pesticides.

Supercritical Fluid Extraction

Supercritical fluid extraction (SFE) is a technique that became popular during the 1980s.[130] Generally speaking, supercritical fluids (SFs) are gases with high density above their critical temperature and pressure that exhibit simultaneously properties associated with both gases and liquids.[131–133] Thus, like gases, they are compressible, but they also display solvencies similar to those of the liquids.

As the name suggests, supercritical fluid extraction (SFE) employs supercritical fluids for extraction purposes in place of the organic solvents of conventional extraction. Any increase in temperature at constant pressure reduces the solvent power of a supercritical fluid, but it also leads to an increase of the diffusion rate, which tends to lower the minimum required extraction time. Compared to conventional extractants, supercritical fluids have low viscosity and have diffusion rates that are higher by a factor of 10 to 100, both of which contribute to reduce the extraction times. Moreover, analyte melting points and solubility in the SF are important properties to

consider.[132] With supercritical CO_2 and N_2O,, which are gases under normal conditions, the extractant is separated by reducing the pressure to atmospheric levels, leading to simultaneous concentration of the extract.

Supercritical CO_2 is the most frequently used extractant for SFE. It has recoverable characteristics and the ability to solubilize lipophilic substances.[134,135] It has the advantage of being chemically inert. Its critical temperature is low, so it is acknowledged as a valuable chemical for the extraction of thermolabile analytes such as steroids and fragrances.[136] Other advantages of CO_2 as an extractant include high purity and low cost. The principal disadvantage of CO_2 is a relatively low polarity. However, its solvent power with respect to polar analytes can be improved by adding polar modifiers (or a mixture of them) such as methanol and n-hexane,[137] ethanol,[138] aqueous acetonitrile,[139] or dichloromethane.[140]

Extraction with supercritical CO_2 has been used for separating a wide variety of analytes, including pesticides from food,[141] vegetables,[142] aquaculture and marine environmental samples,[143] vitamins from tablet matrices,[144] PCBs from fish muscle,[145] sediments,[146,147] and powdered full-fat milk.[148]

Solid-Phase Microextraction (SPME)

Solid phase microextraction (SPME) is a simple, rapid, sensitive, and solvent-free sample preparation technique in which analytes in either air or water matrices are extracted into the polymeric coating of a fiber.[19] It was originally developed by Arthur and Pawliszyn in 1990.[149] Subsequently a number of books have been written on the technique.[150–152] The mechanism of SPME is based on the partitioning equilibrium of the analytes between the sample or the headspace above the sample, respectively, and a fused silica fiber coated with a suitable stationary phase. The amount of analyte extracted by the fiber is proportional to the initial analyte concentration in the sample and depends on the type of fiber. After sampling, the fiber can be thermally desorbed directly into the injector of a gas chromatograph. SPME combines sampling, analyte enrichment, matrix separation, and sample introduction within one step.[153] Since its development, this innovative technique has found widespread use in environmental analysis. It has, for example, been applied in the determination of volatile organic compounds,[154] biologically active substances,[155] phenols,[156] pesticides,[157] polyaromatic hydrocarbons, and polychlorinated biphenyls[158,159] in water. In a technical note, the application of the SPME hyphenated with a temperature-programmed desorption (TPD) for the analysis of chemicals with wide-ranging volatilities without causing their thermal degradation is presented.[19] Degradation

is, however, a problem often encountered in the analysis of active pharmaceutical ingredients. Shepard et al. described a complex preparation alternative for the analysis of L-ascorbic acid, a compound which can be degraded in the solid phase under the influence of moisture.[160,161]

SPME fibers have also been used as air sampling devices for volatile organic compounds in ambient and workplace air. The results obtained with SPME were in good agreement with traditional sampling methods.[162,163]

In a detailed review on SPME technique, fibers with different thickness and polarities are presented.[164] Many examples of SPME applications, including direct immersion into a liquid sample and headspace sampling, are presented in a review of food analysis.[165] However, direct immersion of SPME into some natural matrices can be difficult and the fiber can be damaged or some analytes can adsorb irreversibly to the fiber, changing its properties and making it unusable for more than one sample. The use of SPME-LC for the analysis of pesticides was reviewed in 2005.[166] In 2007, the most suitable sample preparation techniques for organic compounds in air and water matrices were also reviewed.[167]

The main advantages of the SPME technique compared to solvent extraction include the reduction in solvent use and the sensitivity for polar and non-polar analytes in a wide range of matrices, when SPME is combined with both GC and LC. The main disadvantage of the SPME is the low storage stability of the samples, due to uncontrolled losses of analytes by adsorption on the walls of the vials or by evaporation from the loaded fiber.

A recent development of the SPME technique is the new superelastic fiber type. This is a metal alloy with elastic properties that can be coated with polydimethylsiloxane-divinylbenzene (PDMS/DVB), carboxen/PDMS and DVB/carboxen-PDMS as well as PDMS. This alternative improves the robustness and overcomes the problems of the breaking of fibers due to misalignment with injection ports or in viscous matrices.[168] Two relatively new reviews include discussion of recent developments that may have significant implications for automation, such as superelastic fiber assemblies and internally cooled fiber-SPME.[169,170] These reviews also describe the recent developments of solid-phase microextraction technology applied to food, environmental, and bioanalytical chemistry.

Stir Bar Sorptive Extraction (SBSE)

Stir bar sorptive extraction (SBSE) technique is a sample preparation tool based on sorptive extraction of interest analytes that can later be removed by thermal desorption in the gas chromatographic injection port. SBSE is a dynamic variation of SPME in which a spinning glass-covered magnetic bar (coated with a thick layer of polydimethylsiloxane) is used to sorb. This technique was developed in 1999 using stir bars coated with

50–300 µl of polydimethylsiloxane (PDMS).[171] The advantage of SBSE is a higher enrichment factor combined with the application range and extraction mechanism of SPME.[172] Transfer of the analyte from the bar is achieved either by GC thermal desorption or by elution with an LC solvent. As with SPME, the stir bar can also be used to sample the volatiles and semi-volatiles in the headspace above the sample. It can be used for liquid or semi-solid complex matrices and, therefore, has potential for many applications in coffee brew analysis[173], in the determination of polycyclic aromatic hydrocarbons (PAH) in aqueous samples,[174] and for the determination of pesticide residues in honey.[175]

There are several articles that compare SBSE with other extraction techniques on different target analytes. Steam distillation extraction,[176] membrane assisted solvent extraction (MASE),[177] and SPME[178] represent some alternative extraction techniques used in different studies, in which the authors concluded that SBSE is more sensitive and affords improved reproducibility and less artifact formation. However, despite good sensitivity, SBSE extraction was not suitable for the analysis of some polar pesticides in food.[179] David et al. gave examples of food analysis by using the SBSE technique and described the analysis of solid samples after an initial extraction with a water-miscible solvent.[180]

Because of the PDMS coating, SBSE is most suitable for the analysis of non-polar analytes from aqueous media. To a lesser extent, it can be concluded that this technique can be used for more polar compounds after a proper derivatization step. Bicchi et al. describe how to improve the recovery of more polar analytes in SBSE and HSSE (HeadSpace Sorptive Extraction) techniques.[173] Applications of SBSE in analysis are increasing, but due to the limitations of the PDMS phase, they are still currently limited to non-polar or semi-polar analytes.[181]

Hollow Fiber Membrane Extraction

The demand for automation in analytical liquid-liquid extraction (LLE) combined with organic solvent reduction or elimination has led to the recent development of liquid-phase microextraction (LPME) based on disposable hollow fibers.[182] This approach has been reviewed by Rasmussen and Pedersen-Bjergaard.[183] This review focuses on basic extraction principles, technical set-up, recovery, enrichment, extraction speed, selectivity, applications, and future trends in hollow fiber-based LPME. In this technique, analytes of interest are extracted from aqueous samples, through a thin layer of organic solvent immobilized within the pores of a porous hollow fiber, into an acceptor solution inside the lumen of the hollow fiber. Subsequently, the acceptor solution is directly subjected to a final analysis by capillary gas chromatography (CGC),

high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), or mass spectrometry (MS) without any further effort. Hollow fiber-based LPME may provide high analyte pre-concentration and excellent sample clean-up, and it has a broad application potential within areas such as drug analysis and environmental monitoring. A simple and easy-to-use extraction procedure has been applied for the extraction of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in urine and spiked plasma samples, using a short piece of narrow capillary-like microporous hollow-fiber (HF) membrane as an extraction device.[184]

Enrichment Techniques Driven by Gas-Liquid or Gas-Solid Equilibriums

The rapidly developing trend of chromatographic analysis foresees the use of the substance to be analyzed as one of the phases of the heterogeneous (usually) gas-liquid system. The analytical and physico-chemical characteristics of the liquid phase (and sometimes solid) are determined by analyzing the gaseous phase, into which some part of the components of the liquid material to be analyzed is partitioning with the establishment of an equilibrium. The name of the method, "analysis of equilibrium vapor" or "vapor-phase analysis" (head-space analysis, HSA) is derived from this equilibrium condition.[185] However, it must be noted that the thermodynamic equilibrium between the phases is not required in all the practical applications. Accordingly, there are possible methods of determination that assume only a certain degree of equilibration. A distinctive feature of the HSA technique is that the chemical information contained in the gas phase is used to determine the nature and composition of the condensed phase with which it is in contact. The development of HSA methods opens up wide possibilities for determining trace contaminants in the atmosphere, in other gaseous media, and in other substances. The features of HSA make it a very effective technique. Two groups of methods of head-space analysis can be distinguished, namely, 1) static methods: when the equilibrium between the gas and the condensed phases is reached within a closed system, and 2) dynamic methods. In the latter, the contact between the phases occurs in an open system in which a flow of gas is passed through a layer of liquid sample or a granulated solid phase, and the volatile analytes (or their derivatives) are purged out of the system.

Static Headspace Technique

The classical HSA methods (including their automated variations) are based on sampling the volatile analytes from an enclosed space in a static system using a gas-tight syringe. Analytes of interest are equilibrated in a

closed vial at a specified temperature and pressure. Use of a gas-tight syringe (or autosampling system) is one of the common techniques used to transfer the headspace sample into the gas chromatograph.

HSA is considered to be a technique directly connected with a gas chromatographic analytical instrument, but it can be used with practically any analytical technique. In fact, the first applications of headspace sampling were not in GC.[185] The main disadvantage of static headspace extraction is the lack of preconcentration. Consequently, this technique is not fully suitable to the analysis of trace and ultra-trace constituents, unless the loss (or the lack of gain) in sensitivity during extraction is compensated by the detection technique.

A brief overview of headspace analysis techniques and the underlying theory has been provided by Snow and Slack in 2002.[186] The paper includes examples of applications in environmental, clinical, forensic, biological, food, flavor, and pharmaceutical analysis.

Headspace-single-drop microextraction (SDME) is a variation on static headspace. Volatile components are trapped on a single drop of solvent that is suspended from the tip of a syringe in the headspace above the sample. Practical difficulties with the technique include a limited choice of solvents due to viscosity requirements, and further work is needed to prove the reproducibility of this technique.[187]

Most of the papers related to HS-SDME deal with the determination of trace polycyclic aromatic hydrocarbons in environmental samples,[188] the analysis of carbonyl compounds in biological and oil samples after derivatization with 2,4,6-trichlorophenylhydrazine (TCPH),[189] and the analysis of volatile halocarbons.[190] Lambropoulou et al. published an analytical application of HS-SDME, which was adopted as an isolation and trace enrichment step prior to the analysis of organic pollutants (pesticides, polycyclic aromatic hydrocarbons, polychlorinated compounds, organotin compounds, and phenolic derivatives, aromatic amines, phthalates, etc.) by gas and liquid chromatography.[191]

Headspace-solid phase microextraction (HS-SPME) is another variation on static headspace that traps the volatile components onto a SPME fiber held above the sample. Such mode of extraction is based on the equilibriums between three phases: sample matrix, vapor phase, and fiber. Interestingly, in conventional headspace analysis raising the temperature increases the amount of analyte in the vapor phase and hence gives improved sensitivity. In contrast, with HS-SPME a higher temperature may result in less deposition onto the fiber as volatile components again favor the vapor phase. In some cases, the peculiar features of HS-SPME can make a definite advantage: in studying the aroma profile of cocoa products, the fiber was proved to be more favorable for the enrichment of lower volatility compounds than the direct headspace.[192] HS-SPME was

also used for the determination of pesticide residues in fruits and vegetables[193] and for the analysis of trihalomethanes in water samples.[194]

Dynamic Headspace Technique

Dynamic headspace is basically a development of the static headspace so that complete removal of the volatile analyte from the HS is accomplished. In principle, the volatile analytes are stripped out of the solution by a carrier gas and then subjected to a pre-concentration step by trapping them on various media. It usually follows a thermal desorption into a gas chromatograph. Such an approach involves, on the one hand, the purging of the analytes and, on the other hand, their trapping and is generally called purge-and-trap injection (PTI).

The major drawback of the dynamic headspace is the limitation to the analysis of relatively volatile compounds with boiling points below 200°C. Also, this technique is expensive and requires a fully dedicated and complex instrument.[186]

Several experimental designs have been developed as trap devices. The needle capillary adsorption trap device, described by McComb et al., is based on a combination of SPME and purge and trap methods.[195] Only limited applications of such SPME devices in dynamic headspace analysis have been published, such as the determination of volatile compounds from aqueous[196] or gaseous samples.[197]

A recent development in headspace analysis is solid phase dynamic extraction, also called headspace-solid phase dynamic extraction (HS-SPDE). In this technique the headspace is repeatedly drawn up into a syringe through a coated needle which traps the analytes. The latter are then desorbed directly into a GC. A variety of sorbents is available including divinylbenzene, carboxen, carbowax, polyacrylate, and mixed phases. This technique has been applied for the trace determination of volatile or semi-volatile analytes in aqueous matrices[198] or in food matrices.[199]

Solid Phase Extraction (SPE)

This technique is used for the selective separation and concentration of analytes from liquid or gas samples and often is used to clean up and concentrate liquid extracts. Therefore, SPE could have been included in Paragraph 5.2 as well. SPE is a technique referring to a non-equilibrium exhaustive removal of analytes (semi-volatiles and non-volatiles) from a liquid sample by retention on a solid phase (sorbent), and to the subsequent elution of selected analytes from the solid phase by an appropriate solvent.[65] The desorption of the analytes from the solid phase can also

occur under thermal treatment. The efficient use of this technique requires optimization of the sorption and desorption processes.

Extraction by SPE is based on the distribution of the analytes between the sample and a solid phase, which is usually contained in a cartridge. Separation of target analytes from complex matrices may be a sum of several synergic effects such as differing polarities, differences in molecular size, and differences with respect to ion-exchange capacity.

Solid-phase extraction (SPE) has several advantages over liquid-liquid extraction (LLE). SPE can be accomplished more rapidly, requires less solvent, and provides more highly concentrated extracts. It is possible to choose among a range of adsorbents that use different mechanisms for the extraction/retention of analytes. The different adsorbents that are applicable in the SPE technique can be classified according to their nature as nonpolar (e.g., those carrying octadecyl, octyl, butyl, cyclohexyl, phenyl, amino and diol groups), polar (e.g., cyano, Kieselguhr, silica gel, Florisil, aluminum oxide), anion exchangers (e.g., primary amine, secondary amine, quaternary ammonium salt), and cation exchangers (e.g., carboxylic acid, sulfonic acid). The most common adsorbents for solid-phase extraction are based on silica gel, the surface of which has been modified in some way.[200]

Octadecyl surface solid-phase (C18) is used for the reversed-phase extraction of nonpolar substances from aqueous solutions. Typical applications include the extraction of organochlorine pesticides,[201] organophosphorus pesticides,[202] chlorinated hydrocarbons,[203] PAHs,[204] phenols and chlorophenols,[205] and antibiotics.[206] Octyl surface solid-phase (C8) is used for extracting substances of medium polarity. Substances that bind irreversibly to C18 phases can often be concentrated and re-eluted successfully with C8 phases.[200]

Unmodified silica gel, aluminum oxide, and Florisil, usually called normal phase materials, separate sample constituents into fractions of comparable polarity. They are often utilized to separate and concentrate pesticides,[207] PCBs,[208] polychlorodibenzodioxins and dibenzofurans (PCDD/PCDFs),[209] and for the simultaneous determination of bisphenol A, triclosan, and tetrabromobisphenol A[210] from biological, agricultural, and environmental samples.

Normal phases are also used to extract polar sample constituents, such as amines, alcohols, phenols, dyes, medicaments, or vitamins.[211,212]

Apart from modified silica gel, the most frequently used solid-phase adsorbents are activated charcoal and resins (XAD). Activated charcoal is a universal adsorbent for concentrating trace organic materials from aqueous solutions and air. XAD resins are also commonly employed for extracting organic trace constituents, such as persistent organic pollutants from the atmosphere.[213]

The activity of these solids must be accurately adjusted to ensure reproducible results and well-defined fractions, and sample solutions must always be carefully dried prior to extraction. One of the drawbacks of SPE is that the packing must be uniform to avoid poor efficiency. The sample matrix can also affect the ability of the adsorbent to extract the analyte due to competition for retention. The limits of many traditional adsorbents in terms of selectivity and insufficient retention of very polar compounds can also be a problem.[214]

A recently developed variant of SPE is the extraction with synthetic molecularly imprinted polymers (MIPs). Thus, retention of analytes on the adsorbent is due to shape recognition in the cavities or imprints. Due to the nature of their selectivity, synthetic MIPs can often be used for a number of matrices, even though the interaction may be different.[215] They can be heated and are stable in both organic solvents and strong acids and bases. However, custom-made products must be prepared for each analyte. Moreover, stringent cleaning of the MIP, prior to trace analysis, is necessary to remove the analyte, which had been used as a template. MIPs have been used as selective adsorbents for a range of analytes and matrices.[216]

As already discussed, SPE is a useful clean-up technique for trace analysis but, usually, it is not employed alone for sample preparation. SPE would rather follow an initial extraction step. Selective adsorbents in SPE are a useful tool for both selective and sensitive analysis of trace contaminants in complex matrices.

CONCLUSIONS

Detection methods are becoming more specific and sensitive. In trace analysis, sample preparation is particularly important as it can account for a significant amount of the variability of a particular method. Thus, sample preparation is a critical step in the overall process of obtaining reliable and accurate data, especially in the trace analysis of nonvolatile and semi-volatile organic compounds. Considering the large number of articles published in the last decade, it can be easily concluded that trends in sampling preparation are focused on the minimization of the use of organic solvents in, automation of, and speeding up of the sample preparation procedure. Some guiding principles can be given depending on the purpose of the analysis, the available amount of sample, the required sensitivity, and the type of sample matrix and analytes to be investigated.

For liquid and solid samples, SPME and SBSE combined with gas chromatographic analysis are good options when the target analytes are nonpolar and volatile. The two extraction methods can also be used for analyzing volatile compounds from solid samples, but only when combined with the dynamic head space technique.

For polar analytes, SPE and LPME are suitable. The big advantage of miniaturized SPE extraction is the minimum amount of sample and organic solvent required, but sensitivity is lower. However, SPE techniques are exhaustive extraction and purification methods, and are suitable for quantitative analysis as well. MAE, also, can be used for the extraction of liquid samples.

For the analysis of volatile compounds, head-space extraction combined with SPME or SBSE are simple and direct options. However, for semi-volatile compounds more exhaustive methods are probably needed.

Nowadays, ASE is gradually replacing Soxhlet extraction. ASE is a good method for the extraction of tightly bound compounds in samples such as sediment and soil. The disadvantage of the ASE extracts is that they typically contain a large amount of undesirable matrix components. Accordingly, a clean-up step of the extract (e.g., by SPE) is always needed.

For samples, in which the analytes are not very tightly bound to the matrix, for example, food, biological tissues, plant, and atmospheric aerosol particles, MAE and USE represent good extractions methods.

The trend of sample preparation is towards automated systems that can be integrated with the final separation step. Presently, a few automated methods are available but only for liquid samples. For solid and semisolid samples, fully automated systems are not available for routine analyses, although several interesting systems have been reported for special applications. For complex matrices, such as biological, environmental, and food samples, a combination of different extraction techniques is often required. However, the objective of any chromatographic method should be to achieve the required performance (e.g., sensitivity, accuracy and precision) in as few steps as possible. Further development is needed to make such systems applicable to large-scale analysis.

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