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Review

Solid-phase trapping of solutes for further chromatographic or electrophoretic analysis

James S. Fritz[a,*], Miroslav Macka[b]

[a]*Chemistry Department, Iowa State University, Ames, IA 50011, USA,*
[b]*School of Chemistry, University of Tasmania, GPO Box 252-75, Hobart, Tasmania 7001, Australia*

Abstract

Because of its simplicity, speed and effectiveness, solid-phase extraction (SPE) has become the preferred technique for concentration of selected analytes prior to chromatographic or electrophoretic analysis. In this review the historical development of SPE is briefly traced. Then the principles of SPE are reviewed in some detail. Numerous references are given on the format, sorbents, elution conditions, online techniques and automation with special emphasis on relatively recent developments. The principles and recent advances in solid-phase microextraction (SPME) are also reviewed. The final section on selected recent applications includes an extensive list of references to work published within the last three years. Future trends and developments are discussed briefly.

Keywords: Reviews; Solid-phase extraction; Solid-phase microextraction; Extraction methods; Sorbents

Contents

*Corresponding author. Tel.: +1-515-294-5987; fax: +1-515-294-3578.
E-mail address: kniss@ameslab.gov (J.S. Fritz).

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1. Introduction

The isolation of selected analytes from complex or dirty samples in a form where further analysis is possible is actually an old and recurring problem. In addition, it is frequently necessary to preconcentrate the analytes to a suitable level. Extraction of aqueous samples with a non-miscible organic solvent, separation into fractions with a rudimentary chromatographic column, Soxhlet extraction, cryogenic trapping of volatile substances, and other techniques have been used for many years. But these methods tend to be slow and labor-intensive. As we begin the new millennium there is a realization that faster and more efficient methods for sample pretreatment are imperative. One study showed that more than 60% of analysis time was spent in sample preparation compared to only about 7% for the actual measurement of the sample constituents [1].

There has also been a growing realization that an increasing percentage of chemical analyses need to be done on a micro scale. The analysis of biomolecules and drug candidates prepared by combinatorial chemistry are but two examples. In this connection, small-scale separation methods such as capillary electrophoresis (CE) and capillary electrochromatography (CEC) are receiving considerable attention.

Solid-phase extraction (SPE) is a particularly attractive technique for isolation and preconcentration of analytes. In SPE typically an aqueous sample is passed through a small tube filled with porous solid particles such as poly(styrene–divinylbenzene) or silica C_{18}. Alternatively, a membrane disk containing sorbent particles may be used. The organic analytes are extracted, usually in a fairly tight band near the top of the extraction tube. After a brief wash, the analytes are eluted by a small volume of an organic solvent. A portion of the eluate can then be analyzed by gas or liquid chromatography, or by capillary electrophoresis.

Solid-phase extraction has several important advantages over liquid–liquid extraction.

(1) SPE is faster and requires less manipulation. A sample can be quickly passed through a SPE column or cartridge with gentle pressure or suction. After a quick rinse, the extracted substances can be washed from the column by a small volume of an organic

solvent or another appropriate eluent. These steps can be automated readily. By contrast, simple solvent extraction requires a considerable amount of manipulation in adding the extractive liquid, shaking, waiting for the emulsion to break, and carefully separating the two liquid phases.

(2) SPE requires much less organic solvent. The large quantities of organic solvents used in analytical separations have become an important environmental concern. Aqueous samples become contaminated with organic solvents and evaporative concentration of the extracts pollutes the air with organic vapors. Proper disposal of used organic solvents has become troublesome and expensive.

(3) SPE is a multistage separation method. It requires only a reasonable difference in extractability to separate two solutes.

(4) SPE provides higher concentration factors. In SPE concentration factors of 1000 or more are often achieved.

Solid-phase extraction may also be done on a micro scale. A technique known as solid-phase microextraction (SPME) has become very popular [2]. In this technique a small fiber coated with a suitable polymer is immersed in a liquid sample with agitation for a certain time period. Sample analytes partition between the sample and the polymeric coating. A fixed fraction of each analyte is extracted. Then the fiber is retracted into a needle housing, the needle is inserted into the injection port of a gas chromatography (GC), and the sample components are thermally desorbed into the GC. Advantages of this method are simplicity, micro-scale extraction and the complete introduction of extracted substances into the GC.

The principles and methodology of solid-phase extraction for sample preparation and preconcentration are covered in this review. The goal is to give the analytical practitioner an appreciation of the practical uses of SPE. The review concludes with a selected list of recent applications.

Two books on solid-phase extraction have been published recently [3,4]. A third book deals with solid-phase microextraction [5]. A comprehensive review article by Hennion [6] provides updated information about new SPE materials, their interaction mode and their potential for modern applications.

2. Historical development of solid-phase extraction

Around 1970 the water supplies of cities and towns were commonly analyzed for hardness and biological organisms; very little was known about the organic compounds that were naturally present or that were present because of contamination. Pesticides were sometimes determined by adsorption on a bed of activated charcoal, followed by elution with chloroform. The severe limitations of this carbon adsorption method (CAM) have been documented [7]. Often only a low percentage of the organic pollutants are taken up from water samples and not all of the compounds adsorbed are subsequently eluted by chloroform.

In 1972 Burnham et al. [8] published the results of an investigation of the pollutants in the water supply of Ames, IA (USA) which had an undesirable taste and odor when certain wells were used. The method used was called the porous polymer method. As much as 150 liters of water was passed through a column filled with Rohm and Haas XAD-2 (porous crosslinked polystyrene particles) at a rate of 4.0 bed volumes/min. The extracted organic pollutants were then eluted by passing 15 ml of diethyl ether through the column. The ether effluent was carefully evaporated to <1 ml and the individual compounds separated by gas chromatography. The following compounds were found to be in water from a contaminated well at concentrations ranging from 1.7 to 19.3 parts per billion: acenaphthalene, 1-methylnaphthalene, methylindenes (two isomers), indene and acenaphthalene.

In 1974 a comprehensive study of the porous polymer method was published [9]. This paper was later identified as one of the twenty most-cited papers ever published in the *Journal of Chromatography* [10].

The test results for a total of 85 different organic compounds were reported in the 1974 paper. Several compounds were studied from each of the following classes: alcohols, aldehydes and ketones, esters, polynuclear aromatics, carboxylic acids, phenols, ethers, halogen compounds, nitrogen compounds, and pesticides. As stated in the report, ‘‘The results indicated that the procedure is reliable and accurate, and the porous polymer method can be used with

confidence for analysis of natural waters of unknown composition''.

So, for the first time a detailed and widely applicable analytical method was available for extraction of organic compounds from aqueous samples. Extremely low concentrations of organic compounds are quantitatively taken up and subsequently eluted by a small volume of an organic solvent. The method was a tremendous improvement over the charcoal adsorption and solvent extraction methods that were previously used.

In addition to providing a detailed study of the various steps in the analytical determination the 1974 paper gave useful information on methods used to prepare standards of organic test compounds and in proper ways of handling samples prior to analysis. Even the shape of the container used to evaporate the eluting solvent was found to have a major impact on the quantitative aspects of the method. In the following years there was a veritable explosion of information regarding the pollutants present in various waters [11–14].

The porous polymer method was the forerunner of modern solid-phase extraction. However, practical use of the XAD porous polymer method in the 1970s and the 1980s was undoubtedly limited by the lack of high surface area solids available commercially in a purified form of suitable particle size. Many scientists did not wish to grind, sieve and purify their own resin. During the 1980s this situation was remedied and a wide variety of sorbents and the associated equipment for SPE became available. There was also a growing realization that SPE greatly speeded up sample preparation, which had previously been the slowest step in the analysis of many types of samples.

3. Principles of solid-phase extraction

3.1. The four steps of solid-phase extraction

3.1.1. Conditioning

Before extraction of analytes can begin, the sorbent bed must be prepared so that it will make intimate and effective surface contact with the liquid sample solution. Most commonly, conditioning is accomplished by passing a small volume of methanol or acetonitrile through the SPE extraction tube. Some of this organic solvent is adsorbed on the surface of the sorbent particles, making the surface more hydrophilic and thus more compatible with a primarily aqueous sample solution. Without such treatment the surface of many common sorbents is hydrophobic and is poorly wetted by the hydrophilic sample solution. The polar liquid flows in small channels through the solid phase without making the necessary close surface contact. The conditioning step also serves to elute any adsorbed organic impurities from the SPE bed.

3.1.2. Adsorption

The liquid sample is passed through the packed SPE device with the aid of a gentle vacuum (applied to the end of the column), applied pressure or a pump. The flow rate should be reasonably constant. The flow rate and sorbent bed dimensions will depend on the particle size of the solid extractant. Very small particles (e.g., ~10 μm) are more efficient than columns packed with larger particles (e.g., ~50–100 μm). Therefore, a smaller bed of the smaller particles may be used.

3.1.3. Washing

The most common type of SPE is where organic analytes are extracted from an aqueous sample. The purpose of the washing step is to remove salts and other nonextracted material as completely as possible without eluting any of the desired analytes. Water alone is often the appropriate wash solution, but some solutes may be partially retained by the SPE column and only slowly washed off by water alone. In such cases water containing 10–20% of an organic solvent might be a better wash liquid. Of course, the wash solution must not contain a percentage of organic solvent high enough to elute the sample analytes.

3.1.4. Elution

In the elution step the adsorbed analytes are removed from the solid extractant and are returned to a liquid phase that is suitable for analytical measurement. Most commonly, the eluting phase is an organic liquid, although it is often possible to

thermally desorb analytes with the aid of a gas stream. It is usually better to select an eluting solvent that is miscible with water, otherwise the effluent may contain two liquid phases. It is common practice to remove as much of the water as possible from the column just before the elution step. This can be accomplished by applying gentle vacuum for a few minutes or by passing compressed air or nitrogen through the column. Occasionally centrifugation is used to remove liquid from the column.

The eluting solvent should initially be added slowly and carefully to the now dry resin bed in order to avoid channeling. The eluting liquid should be chosen carefully. The most important thing is to select a liquid that will elute the analytes completely from the solid phase using as small a volume as possible of the eluent. In terms of capacity factor, this means that k of the analytes should be as near as possible to zero.

There are several other important considerations. The eluting solvent must be compatible with the analytical measurement methods to be used. For example, when gas chromatography is to be used, the eluting solvent should have a fairly low boiling point so that the large solvent peak will not interfere with the sample peaks. The eluting solvent should be mostly free from impurities that might give disturbing chromatographic peaks. Finally, it should be low in cost and nontoxic. Proper disposal of toxic organic wastes is becoming a costly proposition

3.2. Format

SPE with bonded-phase (BP) silica particles may be carried out in pre-prepared cartridges, in pre-packed tubes of varying dimensions, or in various devices in which the silica is incorporated in a disk. The basic design of cartridges has changed little since their introduction in the late 1970s. A typical cartridge consists of a polyethylene body with a female luer tip at the top for attachment to a positive-pressure source and a male luer tip at the bottom. The packing material is held in place by a 20-μm polyethylene frit at each end. The particle size of the packing material varies, but typically averages around 40 or 50 μm in diameter. The dimensions of the sorbent bed are small enough to permit easy flow of the sample through the cartridge, either by gravity or by suction-aided flow. The small dimensions also minimize the volume of organic solvent needed to condition the column and elute the sorbed analytes.

Prepacked SPE tubes are also very efficient and easy to use. They seem destined to replace the older cartridges. A typical SPE tube consists of a syringe barrel packed with 40–50 μm sorbent material. There is a male luer tip at the bottom and the packing is held in place by polypropylene frits. SPE tubes are fairly low in cost and are disposable. A wide variety of SPE tubes is available from chromatographic supply houses. Sizes range from 1 ml to 60 ml and the weight of sorbent in the tube from 0.1 to 10 g. Bonded-phase silica packings are the most common but tubes packed with various polymeric and carbonaceous sorbents are also available.

Any filtration method may be subject to clogging by small particles of foreign matter. This reduces the flow rate and prolongs the SPE. Depth filters containing diatomaceous earth or a special type of small glass beads are available to reduce clogging. The trend is to integrate filters in the SPE tubes.

Resin-loaded disks are the most convenient format for most types of SPE. These are membranes of polytetrafluoroethylene (PTFE) fibrils impregnated with small particles of solid sorbents such as C_{18} silica or poly(styrene–divinylbenzene). They are manufactured by 3M (St. Paul, MN, USA) under the trade name of Empore. Approximately 90% of the mass of the membrane is made up of the sorbent particles. The particles are close together in the membrane but not necessarily touching one another. The resin-impregnated membranes are flexible and generally are ~0.5 mm thick.

Another type of disk has become available with the sorbent particles trapped in a glass fiber matrix. These are thicker and more rigid than PTFE disks with faster flow rates, and may require no supporting device [15].

Flow rates as fast as 200 ml/min through these membranes are possible when used as 47-mm disks in a suction filtration device. Nevertheless, uptake of organic solutes is very efficient because of the fast extraction kinetics. The resin particles are firmly immobilized within the membrane so that channeling does not occur even though the membrane thickness

may be <1 mm. Studies with very dilute solutions of a dye show that the dye is taken up by the uppermost part of the membrane. The dye uptake is very even over the entire area of the circular disk.

Elution of sorbed analytes from SPE membranes is also fast and efficient. Owing to the very small bed height in a membrane, the amount of organic solvent needed in the desorption step is generally less than with SPE cartridges or mini columns.

Dombrowski et al. [16] studied membrane disks containing anion-exchange resins. Capacity is affected by the surface-area to volume ratio (SAVR) and by the efficiency of mass transfer taking place. They found a SAVR of 0.49 for polymer loaded membranes (PLMs) compared to SAVR of 0.10 for conventional SPE packing — a 5-fold advantage for PLMs. Much smaller particles could be used with PLMs than with conventional SPE packings, allowing for more effective contact with the available surface area. The time for diffusion to the particle surface before the analyte passes through the PLM was calculated to permit flow rates as fast as 500 ml/min.

One of the newest formats of disk technology is a device containing 96-well plates. Small tubes fitted with resin loaded disks are placed in 12 rows of 8 tubes each. A manifold provides enough suction for the samples to pass through the disks. In the elution step the eluate is received in well plates below the SPE tubes. Automated plate handling systems are sold by several manufacturers (Empore, Ansys, Diagnostic, Whatman and Quiagen). The elution step typically requires 100–200 μl of solvent. The time needed to process 96 samples is reduced to <1 h.

3.3. Sorbents

A large number of solid particles have been used for SPE. The most common type of solid-phase extraction is reversed-phase SPE. Here the goal is to isolate relatively nonpolar organic analytes from a predominantly aqueous sample. This requires the use of relatively hydrophobic adsorbent particles such as silica with bonded octadecylsilane groups, porous organic particles such as highly crosslinked polystyrene, or various types of activated carbon or graphitized carbon materials. Following the extraction step the retained analytes are eluted by a small volume of an organic solvent.

A less common form may be termed normal-phase SPE. This technique is used to isolate polar compounds from a nonpolar sample. For example, polar analytes may be extracted from a vegetable oil by adding hexane to make the sample solution more hydrophobic and then passing the liquid through a bed containing a very hydrophilic sorbent. Alumina and various types of silica gels are often used in normal phase SPE. The extracted analytes are finally eluted by a polar solvent such as water or an alcohol.

A third type is called mixed-mode SPE or ion-exchange SPE. The solid particles contain cation- or anion-exchange groups that retain ionic analytes or analytes that can be converted to an ion by a change in pH. However, these particles may retain analytes by adsorption as well as by ion exchange; hence the name mixed-mode SPE. Analytes that are retained solely by adsorption are eluted by a suitable organic solvent, while those retained by an ion-exchange mechanism are best desorbed by an acidic or basic eluent that converts the analyte ions back to their molecular form.

3.3.1. Properties of solid-phase extraction sorbents

High surface area. The uptake of an analyte is affected by an equilibrium between the sample solution and the solid sorbent particle. This equilibrium is shifted more strongly toward the solid phase as the surface area becomes larger. The SPE particles most used have a surface area between about 400 and 1000 m^2/g and at least two (Merck LiChrolut EN and Machery-Nagel Chromabond HR-P) have a surface area of around 1200 m^2/g.

Of course surface area is not the only factor that influences the equilibrium of analytes between the liquid and solid phases. The chemical nature of the solid adsorbent must be such that the analytes equilibrium will strongly favor the solid phase.

Reversible adsorption. Strong retention of analytes by the solid extractant is of course only one half of the desired process. The adsorbed substances must be easily and completely removed in the elution step. In most cases complete elution is obtained by washing the SPE tube or cartridge with a small amount of a suitable organic solvent. However, activated carbon, the first medium to be used for

extraction of organic solutes from water, often adsorbed solutes irreversibly so that subsequent elution was incomplete.

Low, leachable impurities. It is vital that the particles used for SPE are pure and as free as possible from impurities that might be leached during elution of the retained sample constituents. This was a major problem in the 1970s and 1980s when Rohm and Haas XAD resins were used for SPE. At that time crushing and sieving was necessary to reduce the particle size. This exposed new surfaced and released ethylbenzene, benzoic acid and other impurities trapped within the resin during the polymerization step. The detection limits of sample constituents to be determined after SPE are of course limited by the amount of background impurities leached from the solid extractants.

With the excellent products available today this problem is considerably ameliorated. However, sorbent materials readily adsorb impurities from air as well as from water, and must therefore be handled with some care. A short preliminary wash with organic solvent serves to remove and adsorb impurities. Impurities can come from sources other than the particles used in SPE. Junk et al. [17] listed impurities leached from the frits and cartridge housings often used in SPE.

Good surface contact with sample. Extractant particles need to have considerable hydrophobic character as well as high surface area to be efficient for SPE of most types of organic analytes. The problem is that hydrophobic solids tend to be incompatible with aqueous samples. This condition results in poor interfacial surface contact and inefficient extraction. For some years pretreatment of SPE materials with an ''activating'' solvent such as methanol, acetone or acetonitrile has been used to provide better surface contact with the aqueous sample solution. However, if the SPE column runs dry during a run the transiently adsorbed organic solvent may be removed and very low recoveries obtained for sample analytes.

A better approach is to make the surface of extractant particles permanently hydrophilic through a chemical reaction. This provides excellent interfacial contact but the more hydrophobic resin matrix below the thin surface ensures good extraction of organic analytes. Sun and Fritz [18] introduced an acetyl, hydroxymethyl or cyanomethyl group onto the surface of crosslinked polystyrene resins. The derivatized resins could be used without any pretreatment with an ''activating'' solvent. Mild sulfonation of resins also increased their hydrophilicity and makes them wettable with water alone [19]. Several other materials have been produced that can be used for SPE without any pretreatment [20–22].

3.3.2. Bonded-phase silica sorbents

Bonded-phase silica materials are the dominant sorbents used in SPE. In part, this is a carry over from liquid chromatography where the use of octadecylsilane silicas (ODS) is well established. It was a relatively easy task for manufacturers to offer these materials in a form suitable for SPE. For many years *n*-alkylsilicas had been used as the universal SPE sorbent and the possibilities of varying the chemical nature to obtain better selectivity were largely ignored. This has now changed. Some increase in the retention of aromatic analytes has been observed with chemically bonded phenyl phases [23]. Selective silica materials with electron-donor and electron-acceptor properties have been prepared for hydrophobic analytes such as polychlorodibenzo-*p*-dioxins or polychlorobiphenyl cogeners [24]. Cyclopropyl silica sorbents are useful for SPE of pesticides [25]. Aminopropyl silica is an extremely polar sorbent. It has been used for extraction of vitamin metabolites from plasma and other biological samples [26].

It should be recognized that the sorptive properties of silicas vary with the percentage of carbon in the bonded phase and whether the sorbents are endcapped. Residual silanol groups are quite polar, in contrast to the hydrophobic bonded groups. The trend is to minimize the number of residual silanol groups by carrying out the bonding reaction with a trichlorooctadecylsilane and then endcapping any remaining silanol groups by reaction with a highly-reactive trimethylsilane. New types of alkyl silicas have also been prepared by bonding with an alkyl-chain reagent containing an embedded polar carbamate or amide functionality. In this case residual silanol groups are shielded from interaction with polar analytes [27–30].

Although bonded-phase silica sorbents are generally considered to be satisfactory for use in SPE, the percentage recovery of analytes is frequently lower

than with polymeric sorbents. Hennion and Coquart [31] compared several types of extractants by measuring retention factors of analytes in a series of methanol–water solutions and obtaining their values in water alone (k_w) by linear extrapolation.

The k_w values for moderately polar compounds (aniline, benzoic, phenol, etc.) as well as more hydrophobic organic analytes were consistently higher with Hamilton PRP-1 (a crosslinked polystyrene) than with C_{18} silica.

Three questions are of paramount importance in SPE:

(1) How complete is the extraction?

(2) How complete is the desorption of extracted analytes in the elution step?

(3) How great is the concentration that can be obtained?

For a complete extraction the sorptive capacity of the solid-phase extractant must of course be adequate to handle the sum of the analytes. While sorptive capacities may vary widely, the weight of sorbent must usually be at least 1000 times the total weight of analytes. For example, a 10-ml sample containing a total analyte concentration of 10-μg/ml would require 100 mg or more of solid sorbent.

Assuming that the total adsorptive capacity is adequate, distribution of the analytes between the liquid sample and the solid SPE phase must strongly favor the latter. This equilibrium may be expressed by the retention factor, k, of each analyte. If the mobile phase is water alone (rather than a mixture of water and an organic solvent) the retention factor is often written as k_w. In liquid chromatography the retention volume (V_R) of an analyte peak is given by the equation:

$$V_R = V_o\,(1 + k) \tag{1}$$

where V_o is the volume of liquid within the column and detector system.

In SPE the sample itself is the mobile phase. When a sufficient amount of sample has passed through the SPE column, the analyte begins to emerge in a concentration profile much like that of the first half of a chromatographic peak. The point at which the first analyte leaves the column is called the breakthrough volume, V_B. The retention volume (V_R) is the volume at which the analyte concentration in the eluate is one-half that in the sample. It is difficult to define V_B precisely but a convenient estimate from plate theory is:

$$V_B = V_R - 2\sigma \tag{2}$$

where the width of an entire chromatographic peak is 4σ and 2σ therefore represents the width of the first half of a peak, which is the elution pattern in SPE.

From Eq. (1) V_R and hence V_B [Eq. (2)] will depend strongly on the retention factor, k_w. A desirably high V_B requires that k_w be as high as possible. The value of V_B will also depend on SPE column efficiency, as expressed by 2σ. A SPE column evenly packed with sorbent of small uniform particle size will favor a larger V_B. Actually, the efficiency of SPE in terms of 2σ is often not very good; a typical cartridge has been estimated to have only about 20 theoretical plates [32]. One reason for this is that the particle size of a typical commercial SPE device is 40–50 μm, compared to 3 or 5 μm in an HPLC column.

The breakthrough volume as a function of k_w and column parameters can be estimated as follows. Suppose that we have a SPE tube with a dead volume (V_o) of 0.4 ml. V_R is easily calculated by Eq. (1). For $N = 20$ theoretical plates, σ^2 and 2 can be calculated from Eq. (3).

$$N = (V_R)^2/\sigma^2 \tag{3}$$

Then V_B is calculated by Eq. (2). These values are given for a wide range of k_w values in Table 1. The value of V_B is an estimate of the sample volume (V_s) that can be used with essentially complete extraction of an analyte with a k_w value listed in the table.

The concentration factor (CF) is defined as the ratio of sample volume (V_S) to elution volume (V_E). A good eluting solvent should have a retention factor (k) of 1.0 or less. Substituting into Eq. (1) the elution

Table 1
Calculated parameters for SPE as a function of k_w

k_w	V_R (ml)	2σ (ml)	V_B (ml)	CF
10	4.4	2.0	2.4	1.5
20	8.4	3.8	4.6	3
50	20	9	11	7
500	200	89	110	70
5000	2000	895	1105	690

volume should be 0.8 ml. However, twice this amount will be needed to elute the entire analyte peak, giving a V_E of 1.6 ml. This value was used to calculate the CFs listed in the final column of Table 1.

Since a major goal of SPE is to obtain a high concentration factor it becomes important to select a SPE system that will give k_w values that are as high as possible. But what is to be expected in actual practice? Table 2 lists k_w values selected from Braumann [33] for various solutes with a sorbent of the most widely used type, a bonded-phase silica. While halogenated benzenes, alkylbenzenes and fused-ring aromatics have high k_w values, more polar organic analytes have much lower k_w values. This means that recovery of these compounds by SPE will be less than quantitative or the permissible concentration factors will be very limited. Hennion [6] noted similar limitations with silica-based sorbents and found that for many organic compounds the solutes are 10 to 40 times more retained by a polymeric sorbent such as Hamilton PRP-1.

3.3.3. Organic polymeric adsorbents

Polymeric resins with high surface areas are now available in disposable cartridges from several manufacturers. As little as 200 mg of adsorbent provides essentially quantitative recoveries of organic analytes from a sample volume up to 1 l. In many cases the percentage recovery is significantly higher than with bonded phase silica particles. Unlike silica particles, organic polymers can be used at virtually any pH and they contain no troublesome silanol groups.

Table 2
Retention factors in water (k_w) for various solutes using a C_{18} silica column. Data selected from Braumann [33]

Compound type	k_w
Anilines	13–63
Phenols	20–1000
Polar benzenes	
Acetophenone	63
Benzyl alcohol	20
Benzaldehyde	50
Benzonitrile	63
Nitrobenzenes	50–250
Alkylbenzenes	125–40 000
Halogenated benzenes	200–25 000
Fused-ring aromatics	2000–100 000

Until recently most polymeric sorbents were cross-linked polystyrene and required a pretreatment with methanol to make the hydrophobic surface more compatible with aqueous samples. However, polystyrene resins with hydroxymethyl or acetyl substituents on the benzene rings give a more polar surface that functions well in SPE without a methanol pretreatment [18]. These substituents also increase the recoveries of phenols and other polar analytes in SPE.

Introduction of sulfonic acid groups into polystyrene resins at concentrations between 0.4 and 1.0 mequiv./g also provides a hydrophilic surface while retaining the ability to extract organic analytes [34]. These resins can be also used without any methanol pretreatment.

A copolymer of divinylbenzene and *N*-vinylpyrrolidone (Oasis HLB from Waters) is now available in cartridges and a 96-well plate format. The presence of both hydrophilic and liphophilic moities supposedly make this a balanced sorbent. It is capable of extracting acidic, basic and neutral compounds of varying polarities. Its ability to extract relatively small polar compounds (such as catechol) effectively may be explained in part by the ability of the amide group to act as a hydrogen acceptor.

The Oasis adsorbent seems to work particularly well for SPE of selected analytes in biological samples. Recent examples include extraction of basic drugs from acidified human urine [35], diisopyramide from human serum [36], bromo- and chloroacetic acids from tap water [37], omeprazole and 5′-hydroxyomeprazole in human plasma [38], alternariol in tomato paste [39], procainamide and other drugs in serum [40], and carbohydrates in wood, pulp and process liquors [41]. In many of the applications the Oasis sorbent is pretreated with methanol, despite the presence of pyrrolidone groups in the copolymer.

3.3.4. Carbonaceous adsorbents

Activated carbon is one of the oldest adsorbents used for what is now called Solid-Phase extraction. However, the overall recovery (involving adsorption and subsequent elution) is often quite low. A comprehensive comparison of 100 organic test compounds from 13 different chemical classes gave an average 47% recovery using a polymeric resin

(Rohm and Haas XAD-4) but only 18% using an activated carbon [42].

A considerable number of graphitized and other modified carbonaceous adsorbents have become available in more recent years. For example, a product known as Spherocarb is supplied as 100–200 mesh spherical particles with a surface area of approximately 1200 m^2/g. Use of Spherocarb for SPE of 17 organic test compounds gave an average 77% recovery compared to 74% for XAD-4 [43]. However, the polar organic solvents commonly used for the elution step gave low recoveries for many of the test compounds with Spherocarb; only carbon disulfide was found to be a satisfactory eluent.

A porous graphitic carbon (Hypersep PGC) is available in SPE cartridges [44]. Its crystalline structure consists of large, graphitic sheets held together by weak Van der Waals forces. Compounds are retained by both hydrophobic and electronic interactions [45]. This causes very polar and water-soluble analytes to be well retained. Coquart and Hennion [46] successfully concentrated pyrocatechol, resorcinol and phloroglucinol from dilute aqueous samples. Polar compounds such as these normally would be retained very poorly by more conventional SPE materials.

3.3.5. Mixed-mode sorbents

Analytes that are ions, or that can be converted to ions by adjusting the pH, are retained by an ion-exchange mechanism. Commonly used sorbents include silica particles with attached propylbenzene sulfonic acid groups (strong cation exchanger, SCX) or with trimethylaminopropyl groups (strong anion exchanger, SAX). Weak cation exchangers with carboxymethyl groups and weak anion exchangers with aminopropyl groups are also available. Polymeric organic ion exchangers with similar ion-exchange groups are also available or can be prepared by a simple organic reaction such as sulfonation.

Target ions can be retained very strongly by ion exchange. This is illustrated by work in which a toluene solution containing trace amounts of several neutral organic analytes and several carboxylate analytes were passed through a mini column containing ca. 10 mg of an anion-exchange resin [47]. The neutral analytes passed through the column while the carboxylate anions were quantitatively retained. The latter were then eluted by a methanol solution containing 1 *M* HCl to convert the analyte anions back to the molecular form.

Cation exchangers with a high concentration of sulfonic acid groups take up cations but tend to retain neutral organics weakly, if at all, from aqueous solutions. However cation exchangers containing a lower concentration of sulfonic acid groups (ca. 0.5–1.0 mmol/g) can retain neutral organic analytes by physical sorption as well as retaining ionic analytes by ion exchange. This makes it possible to retain analytes by a mixed-mode mechanism.

A simultaneous concentration and group separation of basic and neutral organic compounds from aqueous samples has been obtained with a column packed with a cation exchanger of 0.6–1.0 mmol/g exchange capacity [48,49]. Neutral analytes are retained by simple adsorption, while protonated bases are retained by an ion-exchange mechanism. Simultaneous concentration of organic compounds thus becomes possible from aqueous samples, followed by selective elution of neutral and basic compounds.

The scheme for separating neutral and basic organic solutes into groups is as follows:

(1) The organic solutes are retained by passing an aqueous sample (adjusted to pH 2.0) through a small column packed with a macroporous resin particles with a sulfonate capacity of approximately 1.0 mmol/g.

(2) Neutral compounds are eluted with methylene chloride and the individual compounds determined by GC.

(3) Basic compounds are eluted by 1 *M* methylamine in methanol and the individual solutes separated and determined by GC.

(4) A solution of 2 *M* HCl in methanol is passed through to regenerate the resin. Full experimental details are given in a recent paper [50].

The purpose of the methylamine in the final elution step is to neutralize the protonated organic base cations so that the free base is formed, which is readily eluted by the methanol. The relatively low exchange capacity of the sulfonated resin, as well as the small amount of resin used (ca. 100 mg.), permits neutralization of all of the resin protons with a small volume of $MeNH_2$ in methanol.

Excellent resolution of a number of test com-

pounds into neutral and basic fractions was obtained using this procedure. The recoveries of test compounds were mostly 90–100%.

A similar procedure can be used to concentrate and separate neutral and acidic organic compounds into groups. In this case a macroporous anion-exchange resin of fairly low exchange capacity is used. The resin column is treated with dilute sodium hydroxide to convert it to the OH^- form. The aqueous sample is also made basic to convert the acidic organic solutes to the anionic form. After passing an aqueous sample through the resin column, neutral solutes are eluted with 1 ml of methylene chloride and measured by GC. Then the acidic substances are eluted by 1 *M* HCl in acetonitrile or methanol.

Mixed-mode SPE is particularly useful for body fluids. Conditions are chosen so that drug analytes are held by ion exchange and other organics by simple adsorption. Eluents can be selected that will elute the adsorbed compounds first and then the drugs [51]. Cocaine and related compounds have been determined in urine by a procedure of this type [52]. Determination of airborne volatile amines from polyurethane foams by sorption onto a cation-exchange resin based on poly(succinic acid) is another example [53].

3.4. Eluting solvents

Uptake of analytes is only half of the SPE process. The other half requires complete desorption of the analytes by a small volume of eluting solvent. A considerable number of single organic solvents and often a mixture of two or more solvents have been used for the elution step. The following properties are desirable in an eluting solvent.

(1) A very low retention factor (*k*) for elution of analytes from the SPE particles. If possible *k* should be <1.

(2) The eluting solvent should be as pure as possible to avoid introduction of impurities. A low boiling point is also desirable so that the solvent peak in subsequent analysis by GC will not interfere with the analyte peaks.

(3) Partial or complete miscibility with water is advantageous for smooth elution. Methanol, acetone, acetonitrile and ethyl acetate have been used extensively. Water immisible solvents such as methylene chloride or pentane are likely to form a separate liquid phase from the residual water.

One might think that most organic analytes would be so strongly solvated by a pure liquid solvent that the retention factors for elution from a solid extractant would approach zero. Unfortunately, this is often not the case. A study of retention factors of some 38 analytes from poly(styrene–divinylbenzene) particles gave the following average *k* values: methanol, 1.7; ethanol, 1.3; acetonitrile, 0.45 [54]. Acetonitrile was clearly the best of the three solvents studied and was satisfactory for elution of all the analytes. However, some analytes are more difficult to elute. This is demonstrated by the *k* values in Table 3. Methanol, ethanol and acetonitrile are clearly unsuitable for elution of the PAH analytes other than naphthalene. Tetrahydrofuran (THF) ethyl acetate and methylene chloride are much better.

4. Micro and miniaturized techniques

4.1. Solid-phase microextraction

4.1.1. Introduction

SPME is a micro technique that has caught the attention of analytical chemists everywhere. Simplicity is a major attribute of SPME. In the first step,

Table 3
Retention factors for PAH compounds in organic solvents on poly(styrene–divinylbenzene) columns

Compound	Retention factor					
	MeOH	EtOH	ACN	THF	EtOAc	CH_2Cl_2
Naphthalene	4.7	3.6	1.0	0.5	0.9	0.6
Anthracene	30.0	21.7	5.6	0.5	1.1	0.6
Chrysene	High	High	10.9	0.5	1.2	0.8

a coated fiber is exposed to a sample or its headspace causing the target analytes to partition between the sample and the coated fiber. In the second step the fiber is transferred to an instrument for desorption of the extracted analytes. Usually thermal desorption is used, although desorption by means of an appropriate solvent is also feasible. Subsequent chromatographic analysis enables the extracted analytes to be separated from one another and quantified.

The technique of SPME was invented by Belardi and Pawliszyn in the late 1980s [55]. Since then a large number of papers have appeared on the principles, theory and applications of SPME. An excellent book on this technique was published in 1997 [5]. SPME has been the subject of various reviews [56] and is also covered in at least one other book [57].

The device used for SPME is basically a modified syringe (see Ref. [5], Fig. 2.25). A fused-silica fiber is percolated with a stationary phase of poly(dimethylsiloxane) (DMS) or some other polymer. The fiber is glued to a small stainless steel tube that runs through a syringe needle. The fragile fiber is initially withdrawn into the steel syringe needle, which protects the fiber as the septum of the sample container is pierced. After the sample septum is pierced, the coated fiber is extended into the sample solution for a set time where the analytes are adsorbed by the fiber coating. The fiber is then drawn back into the protective needle and the needle is withdrawn from the sample container. At this point the needle of the extraction assembly is injected into the sample port of a gas chromatograph. Then the fiber is extended and exposed to the heated injection chamber, causing the analytes to be desorbed from the fiber.

The analytes are then focused at the inlet of the capillary GC column. A schematic diagram of a flash SPME injector for GC is given in Ref. [5], Fig. 2.18. A schematic diagram for injection into an HPLC is given in Ref. [5], Fig. 2.26.

In addition to its simplicity SPME has the advantages that only a very small sample is required and that virtually all of the extracted analytes are introduced into the chromatograph. Sharp peaks are obtained and parts-per-trillion detection limits have been obtained with electron-capture and ion-trap detectors [58]. No liquid solvent is required, so solvent disposal is eliminated.

The availability of automated equipment is undoubtedly a key factor in the great popularity. For example, by using a SPME autosampler (Varian, model 8200) the entire process (sample sorption and subsequent thermal desorption) is performed on-line, operator independent and solvent free.

Quantitation in SPME may be based either on an analyte reaching an equilibrium condition between the sample and coated fiber or on non-equilibrium conditions in which a proportional relationship exists between the sorbed analyte and its initial concentration.

Perhaps the most serious disadvantage of SPME is that it is an equilibrium technique. Often, only a small fraction of the sample analytes are extracted by the coated fiber. Quantification is dependent on extracting a precisely known fraction of each analyte. This means that a change in the sample matrix, or any other variable that affects the equilibrium, may affect the quantitative results. By contrast, conventional solid-phase extraction is usually a total-extraction technique, meaning that *all* of each analyte is transferred to the solid extraction phase.

4.1.2. Coatings

A variety of polymeric coatings have been used for SPME. Polymers of dimethylsilane (DMS), various acrylates, divinylbenzene (DVB), Carbowax and copolymers of DMS and DVB are widely used.

Several methods of depositing coatings onto fibers have been used. The dipping technique typically consists of placing the fiber into a concentrated solution of the polymer in an organic solvent. After removal of the fiber from the coating solution, the solvent is evaporated by drying. If desired, the polymer coating can be cross linked.

In another method a piece of hollow fiber membrane (microtubing) made of the desired polymer is used. The membrane is swollen by soaking in an appropriate volatile solvent, the enlarged membrane is placed on the tip of the fiber, and the solvent is evaporated. The thickness of the coating is determined by the membrane thickness.

4.1.3. Experimental parameters

Coating material. The selectivity of a coated fiber can be enhanced by choosing a coating similar in chemical structure to that of the analyte. The sim-

plicity in preparing coated fibers makes it feasible to consider a variety of coating materials.

Coating thickness. A thicker coating will retain more of the target analytes. However, equilibrium with the sample is attained more rapidly when a thinner coating is used.

Agitation method. Efficient agitation of a liquid sample is a practical necessity, otherwise the rate of mass transfer of analytes to the fiber is much too slow. Magnetic stirring is probably the most convenient method for agitation of small liquid samples. Sonication, vortex mixing and other agitation methods have been used.

Owing to a much faster diffusion rate, agitation of gaseous samples is not usually required.

Salting-out effect. Addition of an inorganic salt to the aqueous sample shifts the partition equilibrium so that more of the analytes will be extracted.

pH. As with any extraction method, sample pH can be adjusted to provide better selectivity in SPME. The coating material extracts only compounds that are in molecular form; ions generally are not extracted. An acidic sample pH results in a large enhancement in the extraction of phenols that have a relatively low pK_a value.

Sample heating. Heating liquid samples results in faster diffusion rates of the analytes to the coated capillary surface. This can result in a very significant reduction in the time needed for equilibrium. However, at higher temperatures less analytes is extracted because the extraction process is exothermic.

4.1.4. Kinetics

Slow kinetics can be a bottle neck in SPME unless steps are taken to improve the situation. A comprehensive treatment of SPME kinetics identifies strategies to increase the speed of extractions [59]. It is interesting that the position of the fiber in the agitated sample vial should be kept constant and preferably close to the optimum position, which is about half the distance between the center of the vial and the end of the stir bar. For a given equilibration time, changes in the fiber position may affect the fraction of an analyte that is extracted and thereby cause an error in quantification.

4.1.5. Derivatization

Polar organic compounds present a dual challenge; they are often poorly extracted and after desorption they may be difficult to separate by chromatography. Carboxylic acid analytes are a classic example. Reaction with diazomethane converts them to the methyl esters which are less polar and thus easier to extract and chromatograph. The derivatization reaction may be performed directly in the sample matrix or in the SPME fiber coating.

4.1.6. Quantitation

Quantitation in SPME usually is based on extraction of a known fixed fraction of each analyte and not on total extraction of all the analyte in the sample. The fraction of an analyte extracted (f_{ex}) onto the coated fiber from the sample solution is given by:

$$f_{ex} = \frac{K_d V_2}{K_d V_2 + V_1}$$

where K_d is the distribution, V_1 is the volume of sample liquid phase, and V_2 is the volume of coated phase. In SPME the ratio of V_2:V_1 is usually very small.

Attention must be paid to a number of experimental conditions in order to obtain reproducible results in SPME. Among these factors are: (i) volume of the fiber coating, (ii) moisture in the needle, (iii) temperature, (iv) sample components (salts, organic material, etc.), (v) agitation conditions, (vi) sampling time, (vii) sample volume, (viii) headspace volume, (ix) fiber position in the sampling vial, and (x) injection conditions.

Nevertheless, good precision and dependable quantitation are possible when SPME analyses are carefully carried out.

4.1.7. Headspace SPME

In the basic method used for SPME the extracting fiber is immersed directly into the sample. Another technique is to sample the headspace above a sample in an enclosed container. Use of the headspace mode can avoid one of the major problems of direct-immersion SPME. If the sample is dirty, such as from a sample containing sticky sediments, the fiber coating may be plugged by the sample solids. In such cases SPME may work no better than other SPE

methods. However, sampling the headspace over the sample can largely avoid these problems.

The fraction extracted (f_{ex}) in headspace SPME is given by:

$$f_{ex} = \frac{K_1 K_2 V_3}{K_1 K_2 V_3 + V_1}$$

where K_1 is the constant for the water to air equilibrium of an analyte, K_2 is for the air to coating equilibrium, V_3 is the volume of the coating, and V_1 is the volume of sample. This equation is identical in form to the equation for direct immersion but has an additional K term.

4.1.8. Examples of SPME

A book by Pawliszyn [5] provides a complete list of articles published on applications of SPME through mid-1996. A compilation of more recent references (1998–1999) is given in Table 4. A proceedings issue (Vol. 873, No. 1; 17 March 2000) and a thematic volume (Vol. 885, Nos. 1–2; July 2000) of *Journal of Chromatography A* are devoted to developments in solid-phase extraction.

The addition of salt to aqueous samples to increase extraction is illustrated by the SPME of benzodiazepinc in urine [74] and chlorobenzenes in soil [83]. In the analysis of complex aqueous samples a cellulose hollow fiber membrane with a molecular weight cutoff of 18 000 formed a concentric sheath around the fiber and allowed the diffusion of target analytes with molecular mass <1000 while excluding larger molecules [61]. Gradient elution with water–acetonitrile was used to elute PAH analytes from the extractive fiber with greater selectivity [80].

The use of derivatization to improve extraction is illustrated by the use of pentafluorobenzyl bromide to react phenoxyacid herbicides [78]. Hydride derivatization was used to form methyl mercury in biological samples [84]. A method involving derivitization with a dithiol compound, SPME and GC–MS was developed for the determination of (2-chlorovinyl)-arsonous, the primary decomposition of the chemical warfare compound Lewisite in environmental materials [92].

Headspace SPME is widely used in the analysis of volatile analytes such as trimethylamine in urine [68] biacetyl in wine [66] and various substances in wine that give it a distinctive aroma [76] and bouquet [98]. A poly(dimethylsiloxane) fiber was introduced into a 4 ml box close to a single male asparagus fly. After 1 min exposure, the adsorbed compounds were desorbed and chromatographed to identify the pheromones [88].

4.2. Online SPE–capillary electrophoresis

Capillary electrophoresis has the ability to separate micro amounts of analytes at very high efficiency. Methods that can conveniently combine a preconcentration step with a CE separation will have a bright future. An overview of miniaturized separation techniques with 105 references confirms that miniaturization is a well-defined trend in separation and preconcentration techniques [110]. A nanoscale online device uses a miniaturized 1 mm$\times$50–75 μm reversed-phase extraction device connected without any dead volume to a CE capillary for CE analysis [111].

5. Online and automated methods

Automation of a manual SPE method can provide a much faster sample throughput, improved results and better health and safety. For example, faster synthetic techniques such as combinatorial chemistry have tremendously increased the number of drug candidates available for further investigation. This has put pressure on analytical laboratories to develop much faster methods such as automated, high throughput SPE systems with a pipetting robot [112].

Thurman and Mills [113] have provided an excellent description of equipment that is commercially available for automation of SPE. This includes semi-automated equipment such as workstations, prepstations and devices that perform multiple functions using software tools and dedicated hardware. Equipment for total automation using robotics is also described.

On-line coupling of SPE with HPLC, GC, MS and other measurement techniques is also used. A typical on-line arrangement for SPE–HPLC is easy to perform in any laboratory using simple switching valves and commercial precolumns [114,115].

Typical of the many examples in the recent

Table 4
SPME applications, 1998–1999

Application No.	Subject	Ref.
1	Aroma of wine	[60]
2	Hollow fiber membrane protection	[61]
3	Pesticides in soil	[62]
4	Organic pollutants in air	[63]
5	Homocysteine in plasma	[64]
6	Hydroxyaromatics in water	[65]
7	Diacetyl in wine	[66]
8	Benzodiazepines in urine	[67]
9	Trimethylamine in urine	[68]
10	Aromatic amines	[69]
11	Inorganic mercury, isotope dilution	[70]
12	Landfill leachates	[71]
13	Benzodiazepine in urine	[72]
14	Pesticides in honey	[73]
15	Triazines in soil	[74]
16	Nonionic surfactants	[75]
17	Aroma of wines	[76]
18	Oxygenate and aromatic compounds in water	[77]
19	Derivatization SPME of phenoxy acid herbicides	[78]
20	Benzene/toluene/ethylbenzene/xylenes (BTEX) in indoor air	[79]
21	PAH compounds in waste water	[80]
22	Geosmin and 2-methylisoborneol in water	[81]
23	Flavor volatiles in tomato and strawberry	[82]
24	Chlorobenzenes in soil	[83]
25	Methylmercury in biological samples	[84]
26	Pesticides in citrus fruit	[85]
27	Pesticides in water samples	[86]
28	Amphetamines in urine	[87]
29	Volatile compounds from living flies	[88]
30	Aromatic compounds using a graphite stick	[89]
31	Varietal characterization of wines	[90]
32	Organochlorine pesticides in water	[91]
33	Organoarsenicals in the environment	[92]
34	Cannabinoids in saliva	[93]
35	Local anesthetics in human blood	[94]
36	Decomposition products of erithromycin A	[95]
37	Chlorophenols from landfill leaches and soil	[96]
38	Organic micro-pollutants in air	[97]
39	Wine bouquet components by headspace	[98]
40	Fresh onion volatiles	[99]
41	Chlorobenzenes in environmental samples	[100]
42	Explosives in seawater	[101]
43	Lidocaine in urine	[102]
44	Benzodiazepines in urine	[103]
45	Water-soluble components of slurries	[104]
46	Naphthalenes in water	[105]
47	Ampheramines in human hair	[106]
48	Chlorophenols in urine	[107]
49	Pesticides in aqueous samples	[108]
50	Cyanide in blood	[109]

literature are: a fully automated system for in vivo pharmacokinetic screening [116], automated on-line SPE–GC–MS determination of propoxyphones in hair and whole blood [117], and an automated method for drugs in plasma and serum [118].

Veraart et al. [119] described an automated device for on-line dialysis of biological samples followed by solid-phase extraction coupled to capillary electrophoresis. A membrane with a cut-off value of M_R 15 000 separates a donor from an acceptor channel. The sample is introduced into the donor channel. During a 10-min dialysis period the non-protein-bound analytes pass through the membrane while the higher molecular weight proteins remain in the donor phase. Then a small SPE column serves to preconcentrate the analytes and remove inorganic salts and other possible interferences. The eluate from the SPE column is connected to the capillary electrophoresis system via a homemade interface which is described in the original paper. Six sulfonamides in urine and serum were determined with limits of detection averaging about 100 ng/ml with this system. The method was fully validated and the system was used for more than 500 serum and urine samples without any problems such as clogging the CE capillary or SPE column.

6. On-site sampling; sample archiving

Transporting a relatively large number of water samples back to the laboratory for analysis and preservation of the integrity of the samples can be a problem. Storage of water samples at 4°C has been recommended; small amounts of mercuric chloride are sometimes added to inhibit bacterial growth. Storage space for samples may also be a problem, as in space craft for example.

On-site sampling and preconcentration by SPE is readily accomplished, particularly if extraction disks are used. The disks may be placed in a device where a syringe or hand syringe pump is used to force the sample through the disk. Then the extraction disk can be placed in a small protective envelope and stored until the retained substances can be eluted and analyzed.Several studies have examined the stability of analytes sorbed on disposable cartridges or disks [120–122].

In one study the stability of pesticides on Empore SPE disks for 180 days was better than liquid water samples stored for 130 days at 4°C [123]. Another detailed study compared the recoveries of pesticides stored under various conditions [124]. Captan gave the most dramatic results. Recovery of captan from water stored for 3 days at 4°C was only 28%, whereas the recovery from disks stored at 4°C was 114%. It was concluded that the stability of pesticides was preserved and in most cases enhanced by concentrating the pesticides on C_{18} disks. There was some preference for freezing the disks after the SPE extraction, but disks stored at room temperature generally showed good stability on storage.

Several devices for membrane preconcentration of analytes for CE analysis (mPC–CE) have been described in a comprehensive paper [125]. A membrane impregnated with a chromatographic stationary phase is inserted between two lengths of capillary tubing of the type used for CE analysis. The high adsorptive capacity of the membrane permits loading and analysis of large volumes (10–800 μl) of dilute samples without unduly compromising analyte resolution or separation efficiency. A simple pressurized system is described for sample loading. After loading, elution of the sorbed analytes may require a relative large volume (60–150 nl) or organic solvent. However, when a voltage is applied for CE stacking occurs within the dilute analyte concentrations of the organic solvent zone. Excellent separations were obtained for drugs and peptides by mPC–CE at high concentration factors from the original sample. Analyte detection by MS or MS–MS was possible.

7. Selected recent applications

7.1. Selected samples

A review of selected applications follows. Recent developments and trends are captured in Fig. 1 to Fig. 3. The total number of references for the last five years (1995–1999, Fig. 1) were divided into categories according to the sample type or application area: Biological Fluids, Waters, Forensic, Food, Beverages and Agricultural, Air and gas, and Soil (Fig. 2). This provides a useful division into groups similar to those used elsewhere [1], although some

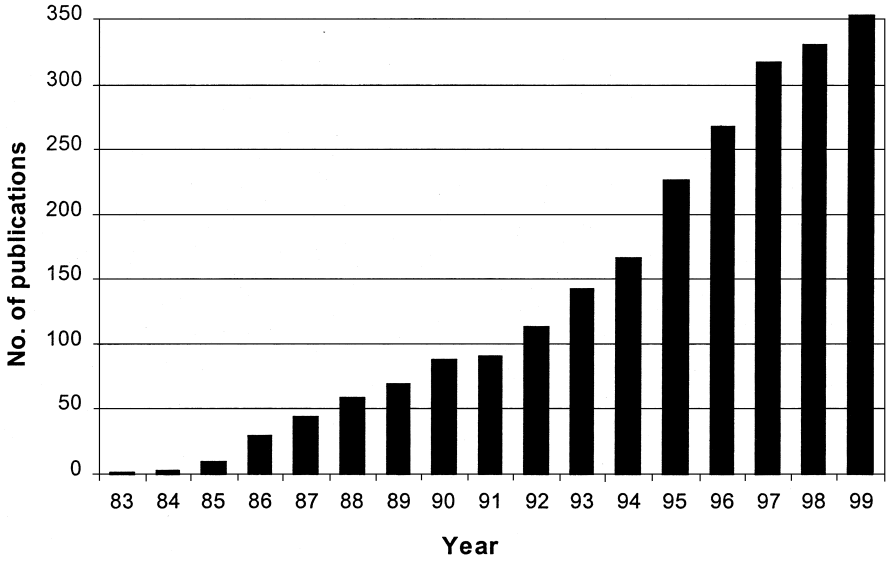

Fig. 1. The total number of publications dealing with solid-phase extraction occurring annually from 1983 to 1999. Source of data: Analytical Abstracts 1980–1999, The Royal Society of Chemistry.

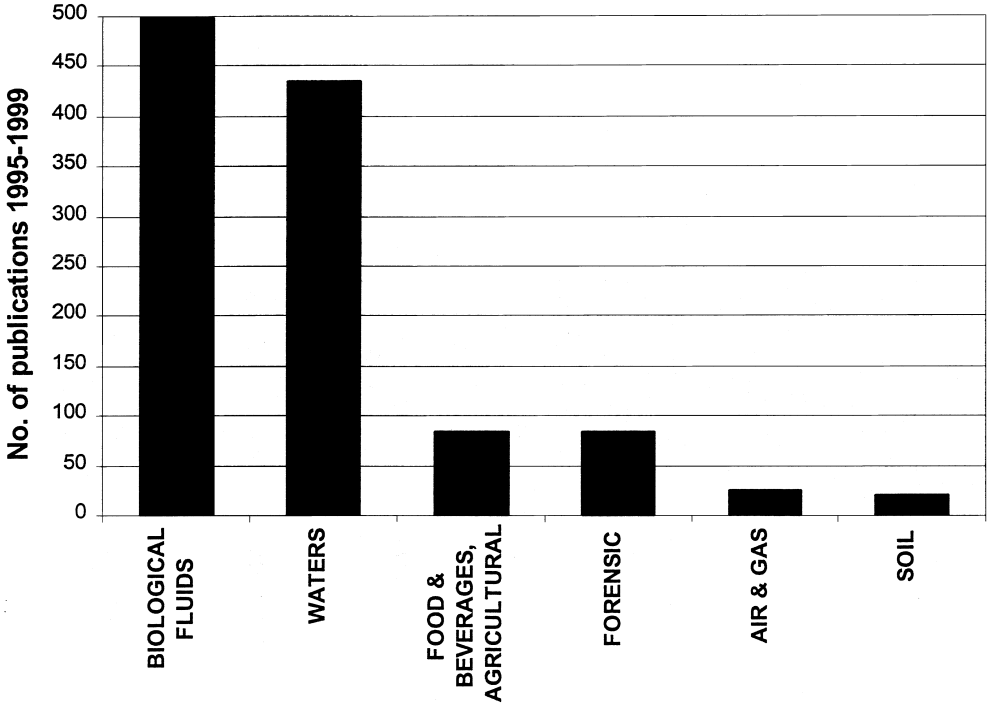

Fig. 2. The number of publications during 1995–1999 dealing with solid-phase extraction according to categories of sample types. Source of data: Analytical Abstracts 1980–1999.

degree of cross-over cannot be prevented, such as for toxicologic analysis (i.e. forensic) in body fluids. Categorization along the analyte type is presented in Fig. 3. By the selection of the publications to be specifically discussed in this section, the following criteria were applied: importance and representativeness of the work in the given application area, novelty of the overall approach or techniques used, and reflection of the new trends of automation and hyphenation, and miniaturization. Focus is given on most recent applications (1999 to beginning of 2000).

First, several review type articles have to be mentioned here, since they dealt with various sample types and therefore would be difficult to order to one sample type category according to the categorization below.

SPME and its use for sample preparation to analyse environmental pollutants in a variety of matrices such as soils, water, and air, including the coupling of SPME to HPLC and CE, was reviewed by Penalver et al. [126]. On-line combination of aqueous sample preparation and GC were reviewed by Vreuls et al. [127]. The approaches comprise heartcut-orientated reversed-phase liquid chromatography–GC and analyte-isolation-orientated analyte extraction–GC and either use techniques in which water is directly introduced onto the GC column, or in which water is eliminated (by solid-phase extraction, solid-phase microextraction or liquid–liquid extraction) prior to introduction of the analytes onto the GC column. The past developments and new trends in SPE and the on- and off-line coupling with HPLC in biological and environmental areas were reviewed by Hennion [6]. Ferrer and Barcelo [128] reviewed the advantages and disadvantages of various sorbents ranging from conventional C_{18} or polymeric, up to recent developments such as immunosorbents (ISs) or molecularly imprinted polymers (MIPs).

Altria [129] published several reviews of applications of CE/CEC to areas including clinical and pharmaceutical, forensic etc. Veraart et al. reviewed the coupling of biological sample handling and capillary electrophoresis and discussed the different modes of solid-phase extraction and the potential of chromatographic, electrophoretic (e.g., isotachophoresis, sample stacking) and membrane-based procedures [130]. Membrane-based sample preparation (dialysis, electrodialysis, filtration and membrane extraction) coupled on-line to chromatography or electrophoresis was review by Van de Merbel [131].

The role of supercritical fluids in separations including supercritical fluid extraction was reviewed by Smith [132].

The review by Pobozy dealt with analysis of trace metal ions and organometallic compounds in a range of samples including waters, urine, sediments, biological tissues and reference materials using on-line combination of SPE and HPLC [133]. Functionalized cellulose sorbents for preconcentration of trace metals in environmental analysis was reviewed by Pyrzynska and Trojanowicz [134] and Vlasakova and Sommer [135] dealt specifically with solid-phase extraction and preconcentration for the determination of trace amounts of platinum group metals in environmental and biotic material.

7.1.1. Biological fluids

Similar to other application areas, the compatibility of SPE coupled with HPLC has been reflected in growing popularity of SPE–HPLC on-line, while SPME–GC keeps dominating the reports from the area of GC. For examples of combinations with GC see [136–146]. A recent example of SPME–GC–MS analysis is the determination of methylated arsenic species in human urine [147].

A number of papers in the area of SPE–HPLC document that it is a well established technique [148–181].

Reports for the combination of solute solid-phase trapping with CE are relatively less frequent and often in an early stage of development [125,182–188]. Petersson et al. [187] described an on-line extractor device consisting of a 1–3 mm length of a 200 μm I.D. capillary packed with 12 μm C_{18} alkyl-diol silica and connected to a 50 μm I.D. separation capillary. The on-line enrichment procedure includes washing, wetting, conditioning, sorption, washing, filling and desorption followed by CE separation. Using the cationic drug terbutaline in an aqueous solution as a model system, excellent separation efficiency (550 000 plates m^{-1} and concentration limit of detection (0.6 n*M*) were obtained. A similar principle was used by Yang et al. [125], however, using miniaturized membranes held

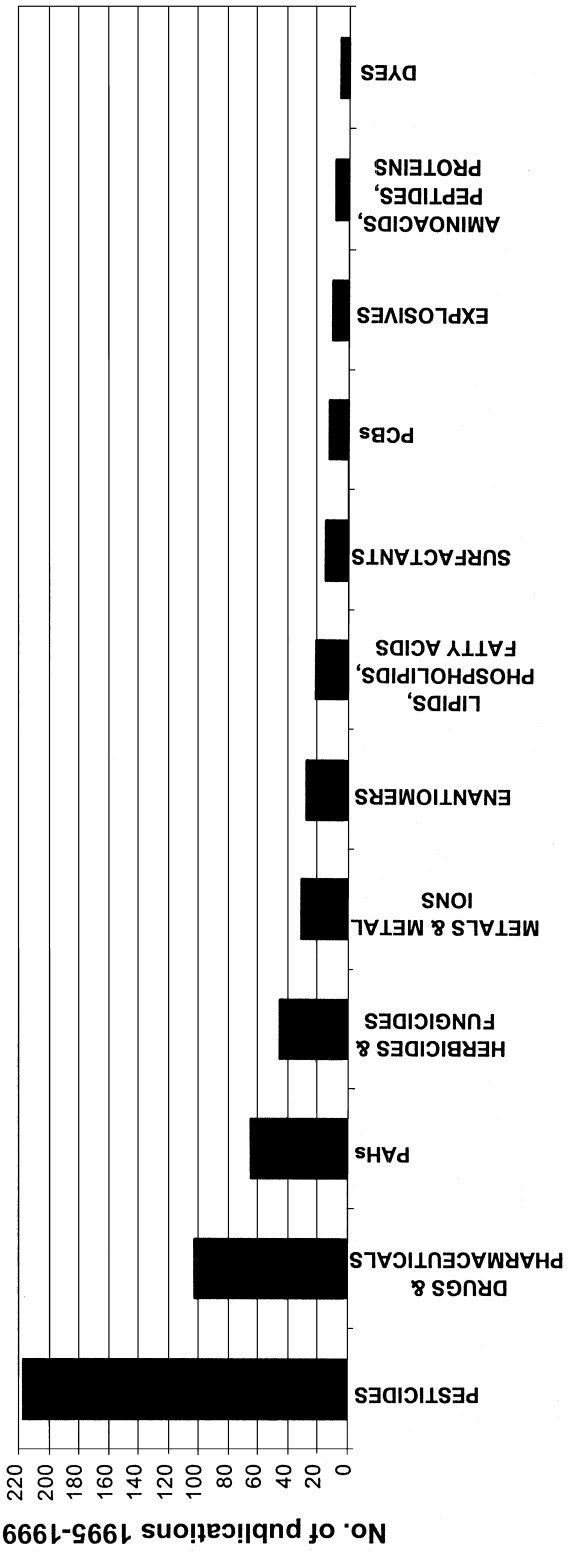

Fig. 3. The number of publications during 1995–1999 dealing with solid-phase extraction according to categories of analytes. Source of data: Analytical Abstracts 1980–1999.

between two pieces of fused-silica capillary instead of miniature preconcentrators column. Rasmussen et al. [188] developed a disposable liquid-phase microextraction device for analysis of drugs in urine or plasma by GC, HPLC or CE. The device consisted of a hollow porous fibre placed into 1–4 ml vial with sample while the fibre was filled with an internal acceptor solution of *n*-octanol (for analysis by GC), or for HPLC–CE with the *n*-octanol immobilized in the pores of the fibre and 0.1 *M* HCl an internal acceptor solution for extraction of basic compounds or with 0.02 *M* NaOH for extraction of acidic compounds. Preconcentration by a factor of 30–125 were achieved after extraction times of 30–45 min.

7.1.2. Waters

An interesting example of a simple combination of sample trapping with a non-separation analytical technique was presented by Ackerman et al. [189] when they determined polycyclic aromatic hydrocarbons (PAHs) isolated from water using SPE combined with a direct in-situ measurement by fluorescence/phosphorescence.

Various pollutants were determined in aqueous samples after SPE or SPME (immersion or headspace) using gas chromatography [flame ionization detection (FID), MS] [190–214] The strength of this technique is nicely illustrated by the determination of ninety pesticides and related compounds in river water by SPE with determination by GC–MS [191]. An example of on-line combination of equilibrium sorptive enrichment using open-tubular traps with GC is the analysis of a group of pollutants varying widely in polarity and volatility in aqueous samples at trace levels [215].

SPE–HPLC was used mostly to analyse for pesticides, herbicides and their metabolites, and surfactants after SPE off- or on-line [65,216–238]. An interesting study was presented by Aguilar et al. [216] who determined a range of pesticides and metabolites using SPE on styrene–divinylbenzene precolumns and on-line HPLC. They also investigated the effect of different storage temperatures (room temperature, 4°C and −20°C) and two storage periods (1 week and 3 months) on the recovery. In general, the recoveries were greater than 90% after 3 months of storage at −20°C. Strong anion exchange resins were used in a method developed by Espinosa et al. [221] for the concentration and speciation of trace amounts of a number of inorganic and organic anionic phosphorus species in soil waters. Concentration of analytes was achieved by passing filtered samples through SAX cartridges followed by eluting with a solution of 0.75 *M* NaCl and 0.5 m*M* EDTA. Separation was achieved by the application of strong anion-exchange HPLC, however, discrete fraction collection and off-line analysis using photometry (reaction with molybdate) was necessary.

SPE–CE/CEC is still presented by relatively few examples [232,239–243]. Hinsmann et al. [240] developed a system using a C_{18} SPE mini-column allowing a 12-fold enrichment of seven pesticides from water spiked at ppb levels. Pre-concentration, elution and injection into the sample vial was carried out automatically by a continuous flow system (CFS) coupled to a CE via a programmable arm. In-line combinations with CE/CEC are mostly at a stage of model studies. Yang and Rassi [243] reported a preconcentration of urea herbicides achieved by a water plug injection followed by a prolonged sample injection onto a ODS CEC column. That was specially designed to have a low surface coverage in octadecyl ligands in order to realize a strong electroosmotic flow and, in turn, fast separations. Using direct UV detection, the determination at 10^{-7} mol/l levels was further lowered to 10^{-10} mol/l levels when the injection was preceded by an off-line SPE preconcentration. An automated system for analysis of common anions was developed by Arce et al. [239] who coupled flow injection to capillary electrophoresis to automate on-line sample treatment for the determination of inorganic ions in a range of samples including industrial waters and waters from water treatment plants.

7.1.3. Forensic

The three major goals of toxicological analysis of a given specimen are: (1) to detect any harmful substances, (2) to identify these substances, and (3) to determine the amounts present. A directed search is designed to detect any of a limited number of substances. An undirected search is also called systematic toxicological analysis (STA). This type of analysis can be defined as the undirected chemical-analytical search for potentially toxic substances whose presence is uncertain and whose identities are

unknown. STA obviously presents a challenge to the analyst. Sample work up procedures should retain all toxicologically relevant substances while removing so far as possible nonrelevant substances and potential interferences.

A review by Franke and De Zeeuw [244] discusses the growing use of solid-phase extraction in STA. An overview is given of SPE procedures using basically three different types of solid phases: diatomaceous earth, poly(styrene–divinylbenzene) and chemically modified silica. Table 3 in this review gives a valuable overview of mixed-mode SPE methods for drug screening in urine, plasma, whole blood and tissue.

Most of the recent reports from the area of toxicological analysis used SPME/SPE in combination with GC. Interesting applications include hair analysis for drugs and drugs of abuse. Girod and Staub [245] analysed for drugs of abuse using automated solid-phase extraction, GC–electron impact ionization MS and GC–ion trap chemical ionization MS. Sporkert and Pragst [246] used headspace solid-phase microextraction (HS-SPME) after hair hydrolysis with 4% sodium hydroxide and in excess of sodium sulfate for the measurement of many lipophilic basic drugs. Analysis of halogenated solvents in the human body is another are of interest [247–249] using HS-SPME and GC–FID [247], GC–electon-capture detection (ECD) [248] or GC–MS [249] for analysis in biological fluids. A model study on two drugs determined in plasma for toxicological applications was presented by Zimmer et al. [250] using automated solid-phase extraction in 96-well plates and liquid–liquid extraction as sample preparation techniques for turbulent-flow liquid chromatography coupled with mass spectrometry.

Another large area of toxicological analysis is the analysis of explosives. Wu et al. developed a SPME-HPLC interface including a 200 μl desorption chamber from a fibre exposed to a stirred sample solution and a Supelco C_8 refocusing unit (3 cm× 4.6 mm I.D.) for the analysis of US Environmental Protection Agency (EPA) 8330 explosive mixture by HPLC with UV detection [251]. In another recent application, Cassada et al. used SPE and isotope dilution LC–atmospheric pressure chemical ionization MS to determine munitions in ground water [252,253].

7.1.4. Food, beverages and agricultural

Food flavor compounds have been traditionally isolated for analysis by distillation, steam distillation, molecular distillation, liquid–liquid extraction, headspace techniques or supercritical fluid extraction. However, the use of SPE in the determination of various chemicals in food has increased rapidly in the last decade and SPE methods have replaced many of the traditional methods of sample pretreatment. A review article discusses this issue in some detail [254]. As an example, the bulk of lipid content of fats and oil in foods has complicated the analysis of pesticide residues as well as other chemical contaminants.

The recent examples of food analysis for volatile flavor compounds show ongoing use of SPE–GC methods but especially an increase in the use of SPME–GC. Examples of the first type of analysis include trace-level determination of polar flavor compounds in butter by SPE with polymeric sorbent and GC–MS reported by Adahchour et al. [255] or multiresidue analysis of pesticides in wines by SPE(C_{18})–GC–MS presented by Wong and Halverson [256]. Examples of the SPME–GC (typically headspace, i.e. HS-SPME–GC) include the analysis of monoterpene composition of essential oil from peppermint [257], volatile flavor compounds of ripening kiwifruit [258], aroma components in orange juice [259], flavor-related compounds in cigarette tobacco [260], or aroma components and volatiles in wines [66,261–265]. Marsili [266] developed an ''electronic nose'' approach for the study of off-flavors in milk using solid-phase microextraction, mass spectrometry, and multivariate analysis (SPME–MS–MVA). Examples of analysis of other naturally occurring substances include SPE–GC analysis of 19 acids and phenols based on anion-exchange disk extraction and in-vial elution and silylation [267], analysis of wax esters in fennel and caraway seed oils by SPE — high-temperature GC–MS [268], or of four isoflavones in plant materials by SPE–RP-HPLC–UV [269].

Another important group of analysis is for pollutants such as pesticides and herbicides or potentially harmful substances. The examples include the analysis of polychlorobiphenyls and chlorinated pesticide residues in mussels using NH_2 and C_{18} Sep-Pak SPE cartridges and GC–ECD [270], pesticide residues in

fruit and vegetables using poly(styrene–divinylbenzene) SPE cartridges and GC with various detectors [271], organochlorine and organophosphorus pesticides in milk by SPE–GC–ECD [272], pesticides residues of 31 pesticides in foodstuffs by SPE and GC–MS or HPLC with fluorescence detection [273], or 31 pesticides of varying polarity in fruits and vegetables by SPE using RP-18-Polar-Plus and cyano material and GC [274]. SPME was used to determine pesticide residues in strawberries using GC–MS (selected-ion monitoring, SIM) [275] and organophosphorus pesticides in fruits and fruit juice by GC–flame photometric detection (FPD) (in P mode) [276]. SPE–HPLC–UV was used to analyse for benzoylurea insecticides residues in grapes and wine [277], phenolic acids and linear furanocoumarins in fruits [278] or for mould metabolite patulin in apple juice and unfiltered apple juice [279]. Other examples are the analysis of teracyclin antibiotics by SPME–HPLC–MS presented by Lock et al. [280] and analysis of PAHs in coffee brew using SPE (C_{18}) and RP-HPLC with fluorimetric detection [281]. A spectrophotometric determination of arsenic in plant materials using flow-injection hydride generation following sorbent extraction preconcentration on ODS minicolumn was reported by Neto et al. [282].

Examples of the application of CE to food analysis come mainly from the field of determination of common inorganic and organic ions such as the analysis of anions in beer and wort by Soga and Wakaura [283], or of biogenic amines in wines by Arce et al. [284]. An example of a successful combination of sample preparation by off-line dialysis with CE is the analysis of a number of common anions and cations in complicated matrixes including milk developed by Kuban and Karlberg [285].

7.1.5. Air and gas

The analysis of air and gaseous samples can be subdivided into analysis of volatile compounds (VOCs) and of particulate matter (PM). The method of choice for volatile organic compounds is either a classical SPE followed by GC analysis [286], or the increasingly popular SPME–GC [287–290]. The examples include the analysis of volatile hydrocarbons [286], volatile organic sulfur compounds [290], field analysis and monitoring of air for VOCs, formaldehyde, and particulate matter [288], indoor air quality monitoring for selected VOCs (carbon tetrachloride, benzene, toluene, chlorobenzene, *p*-xylene and *n*-decane) [287], or personal exposure monitoring to airborne pollutants [289]. Another interesting example in the analysis of air odors is the use of of HS-SPME–GC–MS to study a method for removal liquid swine manure odor presented by Rizzuti et al. [291]. Segal et al. [292] improved the sensitivity of the Chrompack micro-CC system equipped with a thermal conductivity detector by a coupling with a membrane extraction using a sorbent interface, where the sorbent trap has replaced the GC injector. The system was suitable for semi-continuous monitoring of both gaseous and aqueous samples. Detection of less than 1 ppb chloroform in water was demonstrated.

On the other hand, volatiles not amenable to adsorption on hydrophobic sorbents must be adsorbed in a different way, often based on a chemical reaction. An example is the absorption of hydrazine in a ''chromatomembrane'' impregnated with hydrochloric acid solution followed by reaction with *p*-dimethylaminobenzaldehyde and photometric determination [293]. In another example, cyanides in air were preconcentrated in a membrane cell using 0.10 *M* NaOH solution and their content was determined by adsorptive polarography in a pH 8.4 buffer where the cyanide ion forms a quaternary complex with Co(II), α,α'-dipyridyl and ethanolamine. The complex gives a sensitive oscillopolarographic wave at -1.45 V resulting in detection limit in the range of nmol/l [294]. An example of analysis of pollutants present as particular matter in the air is the method developed by Vlasankova et al. [295] for the analysis of platinum group metals (Ru, Rh, Pd, Os, Ir and Pt) after adsorption as ion associates of their chlorocomplexes with *N*(1-carbaethoxypentadecyl)-trimethyl ammonium cation on an ODS column, elution with ethanol and analysis by inductively coupled plasma (ICP) atomic emission spectrometry (AES) or ICP-MS.

7.1.6. Soil

Various pollutants recently determined in soils and soil leachates include hydrocarbons [296–298], polycyclic aromatic hydrocarbons [298,299], phenolic

compounds [300,301], chlorophenols [302], polychlorinated biphenyls [303], herbicides and pesticides [304–309], organotin species [310], organomercuric species [311] and metal ions [312]. The most popular method was SPME–GC [296–298,303,310,311] with detection techniques including MS [296,303], FID [310] and atomic absorption spectrometry (AAS) [311], while other methods included SPE–GC–MS [300,306], SPME–HPLC–electrospray ionization MS [305], SPE–HPLC–UV [304] and SPE followed by X-ray fluorescence [312]. The method developed by Ferrer et al. [304] for phenylurea and triazine herbicides, including some metabolites, applied a layered system of two extraction disks, with SAX styrene–divinylbenzene particles embedded in PTFE as the first disk, and the second disk was a C_{18} disk of 10-μm particles also embedded in PTFE. The purpose of the first disc was to remove the humic and fulvic acids from the water or aqueous soil extract by ion-exchange interactions through their carboxyl groups. Even during methanol elution of herbicides (>90% recovery), the humic substances remain bound to the SAX disk with >85% retention resulting in reducing the interference from the humic acid peak in the LC chromatogram. Another interesting method developed by Espinosa et al. [221] employed SAX SPE, but this time to retain analytes. It was used to carry out speciation of trace amounts of a number of inorganic and organic anionic phosphorus species in soil waters, including orthophosphate, inositol hexaphosphate, glucose-6-phosphate, adenosine 5′-triphosphate, phosphonates and other as yet unidentified forms of phosphorus.

7.2. New development and trends

7.2.1. New entrapment materials

The great popularity of SPME indicates that growth in this area will continue at a rapid pace. A recent modification is called stir bar sorptive extraction (SBSE) [313]. Instead of coated fiber, a stir bar coated with a sorptive polymer is used as the extractant. This simplifies the problem of agitation and the stir bar provides approximately 50× more extractive surface than a coated fiber.

A new technique known as open tubular trapping (OTT) shows some promise. Capillary columns coated with a cross-linked silicone stationary phase are used to extract target analytes from an air sample [314] or water sample [315] flowing through the tube. A long capillary coated with a thick film was originally used but more recently shorter, multichannel devices are employed. OTT is fundamentally different from SPME in that it is not a single equilibrium method. Extraction is by partitioning of the analytes as they move through the capillaries, similar to a chromatographic process. Because of this, essentially complete extraction may be expected. The analytes can then be desorbed thermally with cryogenic refocusing, or by elution with a liquid solvent.

The ability to thermally desorb extracted analytes in SPME is a great convenience. Thermal desorption has been applied to conventional SPE using 4-mm I.D. glass tubes packed with ground up polydimethylsiloxane particles as the sorbent [316,317]. It is likely that other types of sorbent particles will have sufficient thermal stability to be used in a similar manner.

Developments of new solute entrapment materials have to reflect the special needs of solute entrapment materials: capacity, and operation at high flow rates. In that respect developments of new formats of solute entrapment materials such as the membranes and discs are likely to continue. Any impact of the recently introduced ‘‘monolithic’’ chromatographic columns [318–323] allowing operation at relatively very high flow rates on developments of solute entrapment materials is yet to be seen.

The solute entrapment materials operate typically at relatively low separation efficiency and therefore the selectivity plays an important role. Approaches to maximise the selectivity of the solid phase towards the analyte(s) relative to matrix components are represented by two main types of sorbents: (i) affinity, and (ii) molecular-imprinted polymers. The affinity approach has been applied relatively rarely. Kabzinski selectively preconcentrated metallothioneins as markers of exposure to corresponding metals [324]. Brandsteterova et al. selectively preconcentrated catecholamines before their quantification by HPLC–electrochemical detection [325,326]. Probably the most stunning use of the affinity preconcentration was reported by Guzman and coworkers who used affinity sorbents in a miniaturized

capillary column on-line coupled with CE [182–186]. An example of coupling of affinity based preconcentration with GC was shown by Dalluge et al. [327].

The use of molecular-imprinted polymers (MIPs) as adsorbents in SPE has been outlined by Stevenson [328]. Their full potential as materials for SPE is yet to be explored.

7.2.2. Automation

With the increasing costs of labor and demands on analysis speed, the demand for automation in all parts of the analytical method can only grow. Their straightforwardness is the reason for the success of SPME–GC and on-line combinations of SPE various methods, mainly with SPE–HPLC [6], SPE–AAS [329–340] and SPE–ICP-MS or SPE–ICP-AES [341–345].

Apart from the continuation of these now well established and successfully applied approaches, also some new developments were visible. An example of an open-tubular preconcentration column for analyte preconcentration is the system realized by Benkhedda et al. [346] who determined trace amounts of copper and manganese after their preconcentration by flow injection followed by on-line sorption of the analytes in a knotted reactor precoated with 1-phenyl-3-methyl-4-benzoylpyrazol-5-one coupled with electrothermal atomic absorption spectrometry. Efforts to combine sample entrapment and preconcentration on-line with CE is illustrated by the ion-exchange-based preconcentration for the determination of anions by capillary electrophoresis developed by Novic and Gucek [347]. Anion-exchange-based preconcentration technique in which contamination of the sample with the eluent constituents is eliminated is based on elution with hydroxide followed by on-line chemical suppression on a packed-bed suppressor column. The developments in the area of in-line combinations of SPE with CE as outline in the review of Veraart et al. [130] are likely to continue and gain on importance.

7.2.3. Miniaturization

The trends to miniaturization in sample handling are driven by the need to couple sample handling with capillary separation methods, increase the sample throughput, and decrease the consumption of chemicals.

Probably the most successful recent trend in miniaturization was set by the success of the SPME already enjoying a large number of applications. The trends in SPE–HPLC including miniaturization were discussed by Hennion [6].

In CE, on-column focusing onto a stationary phase (such as cryofocusing following thermal desorption as in GC) does not apply and therefore miniaturized in-line preconcentration devices are needed for CE more than elsewhere. However, they are instrumentally demanding and examples limited and mostly in a development stage. Guzman and co-workers used miniaturized in-line capillary preconcentrators with an affinity adsorbent [182,184–186]. Petersson et al. used a 12 μm C_{18} modified silica material packed in a 200 mm fused-silica capillary connected to a 50 mm capillary [187]. Yang et al. used miniaturized membranes held between two pieces of fused-silica capillary inserted in a PTFE sleeve [125].

The chip-based microfluidic devices which are expected to have a huge impact in chemistry, biology and medicine in the future [348–350] have recently started to apply chromatographic principles for sample preconcentration on-the-chip. Kutter et al. [351] demonstrated SPE preconcentration on a chip in a C_{18}-coated channel using a neutral dye for which a 80-fold preconcentration was achieved. Oleschuk et al. [352] presented chip-based CEC with micrometer size ODS coated silica beads which could be mobilized into and out of a cavity using electroosmotic flow through a bead-introduction channel. The potential advantage of this scheme is that the column can be created, removed and re-created, giving a possibility to discard a ‘‘used’’ stationary phase after an analysis of a sample with matrix component(s) irreversibly binding to the sorbent. Using this device, a preconcentration of nonpolar analytes of up to 500 times was demonstrated.

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