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Semi-micro solid-phase extraction of organic compounds from aqueous and biological samples

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Abstract

A technique is described for performing solid-phase extractions on a semi-micro scale. Thin membrane disks 4 mm in diameter containing lightly sulfonated polystyrene or Silicalite particles are placed in the hub of a syringe needle. Aqueous samples (1–6 ml) are passed through the membrane disks and the extracted compounds are subsequently eluted with 20–50 μl of an organic solvent. Unlike solid-phase micro extraction (SPME) which uses a coated fiber, the present method is essentially a total extraction technique. Recoveries >90% were generally obtained for a wide variety of test compounds. The same test compounds in human urine, albumin and human serum samples can be extracted without any pretreatment other than addition of a suitable surfactant. A "double-pass" technique was developed for convenient field sampling.

Keywords: Solid-phase micro extraction

1. Introduction

Liquid–liquid extraction (LLE) has for many years played an important role in sample preparation. However, heightened awareness of the hazards and pollution caused by the use of organic solvents has led to a search for alternative methodologies. Solid-phase extraction (SPE) is an attractive replacement for LLE [1]. For example, SPE is now specified in the drinking water regulations of the US Environmental Protection Agency method 525.1 [2]. SPE is faster, extraction is more complete, and the amount of organic solvent used is but a small fraction of that in LLE.

In a typical SPE method, analytes are simultaneously extracted and concentrated by passing a sample through a cartridge containing appropriate sorbent particles. The analytes are quantitatively eluted off the sorbent with a small volume of organic solvent, typically 1 to 10 ml. The eluate is then analyzed, usually by gas chromatography. SPE is applicable to almost any analyte through the proper choice of sorbent and eluting solvent. Overall, SPE is complete, simple, inexpensive, portable, easily automated and uses relatively little solvent. SPE works well both in an on-line and off-line set up [3].

The use of resin-loaded membranes has been a boon to SPE. In Empore® membranes, solid sorbent particles are enmeshed in a network of Teflon fibrils to form a strong, porous sheet [4]. Membranes require less eluting solvent and are generally more efficient than cartridges containing loose sorbent particles. However, the full advantages of membranes for SPE has not yet been fully realized. Like their cartridge counterparts, membranes are often eluted with relatively large volumes of organic

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solvent, up to 10 ml. To obtain better sensitivity and detection limits, eluates are often evaporated down to a fraction of the original volume. This additional step reduces the speed of SPE and risks the chance of sample loss. Richard and Junk quantitatively eluted pesticides [5,6], polycyclic aromatic materials [6], and tributyltin chloride [7] from C_{18} cartridges using approximately 100 μl ethyl acetate. Since then, elution volumes less than 0.5 ml have been used infrequently.

A technique known as solid-phase micro extraction (SPME) uses a modified syringe housing a fused-silica fiber coated with a gas chromatographic stationary phase [8–11]. SPME involves the partitioning of analytes between the coating and sample matrix, followed by thermal desorption of the analytes into an analytical instrument, typically a gas chromatograph. Although it is truly a micro technique, SPME is an equilibrium extraction technique [10]. Complete extraction of liquid samples is seldom achieved [8] and careful calibration is therefore needed for quantitation.

The goal of the present research was to miniaturize the entire SPE process while retaining the speed and high analyte recoveries obtained with conventional SPE. The semi-micro solid-phase extraction (SM-SPE) system developed reduces sample size to 1–6 ml and the volume of eluting solvent to only 20–50 μl. In addition, SMSPE provides a more compact and portable system that allows easier on-site usage.

2. Experimental

2.1. Reagents and chemicals

Analytes studied were >99% pure and used as obtained from Fisher Scientific (Pittsburgh, PA, USA) and Aldrich Chemical Company (Milwaukee, WI, USA). Laboratory distilled water was further purified using a Barnstead Nanopure II system (Sybron Barnstead, Boston, MA, USA). Sheets of experimental sulfonated polystyrene–divinyl benzene (PS–DVB) resin-loaded membranes, now commerically available as SDB–RPS, and experimental Silicalite-loaded membranes [12] were obtained from 3M Co. (St. Paul, MN, USA). Urine was collected personally and both bovine serum albumin and human serum were obtained from Sigma Chemical Co. (St. Louis, MO, USA).

2.2. Procedure for SM-SPE

The apparatus used for SM-SPE is shown in Fig. 1, which is drawn larger than actual scale to show the details better. The apparatus consisted of a Hamilton 1000 series GASTIGHT 5-ml glass syringe with a Teflon luer lock (Cat. No. 81520) acting as the sample reservoir. The syringe was fitted with fluorocarbon hubbed, 22 gauge stainless steel needles (Cat. No. 90134), which served as the extraction columns. The bottom of each needle was gently tapered to a point by the university machine shop. A piece of stainless steel wire mesh, 4-mm in diameter, 228 μm thick and 53.3% open pore volume, was machined into place just above the tapered bottom to support the membranes. Three needles were used, each containing a different membrane. One needle was packed with the lightly sulfonated PS–DVB resin-loaded membrane, a second with the Silicalite-loaded membrane and the third contained a combination of the two in a mixed membrane. The first two needles were packed by placing a 1×4 mm membrane disk, weighing 9–11 mg, of either membrane into the needle hub. The thickness of these membranes was reduced when the double pass sampling method was used. The mixed membrane needle was

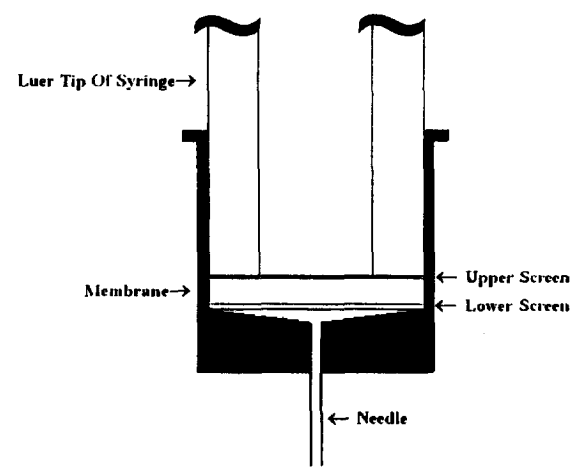

Fig. 1. Device used for SM-SPE. The figure is drawn approximately to scale and enlarged for clarity.

packed by placing a 0.5×4 mm disk of the Silicalite-loaded membrane on top of a disk of sulfonated PS–DVB resin-loaded membrane of the same size. Liquids were forced through the packed needles by pushing down on the syringe plunger. Prior to use, 250 μl acetone and 1 ml deionized (DI) water were passed through to condition each packed needle.

2.3. Single pass sampling

The procedure for loading the membranes was the same for all three needles. The plunger was removed from the syringe barrel and a packed needle locked into place. Samples were prepared by adding a 10-μl aliquot of methanol solution containing 100-ppm each of 2–3 analytes to 1 to 6 ml of DI water. The final concentration of each analyte in the sample was 0.17 to 1.0 ppm. For the mixed membrane experiments, samples were prepared by adding a 10-μl aliquot of a methanol solution containing 50 ppm of each analyte to 6 ml of DI water and adjusting the final concentration of each analyte to 0.083 ppm. The samples were manually pushed through the membranes.

2.4. Double pass sampling

Double pass sampling was used with the two needles containing each membrane separately. To reduce sampling time, the thickness of the Silicalite membrane was decreased to 0.33 mm and the sulfonated PS–DVB resin-loaded membrane was reduced to 0.50 mm. An additional piece of stainless steel wire mesh was placed on top of each membrane to prevent movement. Samples were prepared by adding a 5-μl aliquot of a methanol solution containing 100 ppm each of 2–3 analytes to 1 ml DI water in a capped GC vial. The final concentration of each analyte was 0.5 ppm. The plunger remained in the syringe barrel and a packed needle locked into place. The packed needle pierced the cap septa and a 1-ml sample was drawn up through the membrane. The cap septa was punctured to release air pressure and decrease sampling time. The syringe barrel was immediately emptied by pushing down on the plunger, achieving a double pass through the membrane.

2.5. Elution and quantification

After loading was complete, the syringe barrel was rinsed with approximately 200 μl DI water and air was pushed through the membranes to remove any remaining water. A 20–50 μl aliquot of acetone, ethyl acetate, or methylene chloride was used to elute the compounds into a capped GC vial. An internal standard, 2 μl of acetone solution containing 250 ppm toluene, was added to the contents of the vial, which were analyzed by gas chromatography using manual injection. A Shimadzu (Kyoto, Japan) GC 14A equipped with a flame ionization detector and a C-R4A Chromatopac data analysis system was used to separate and quantitate the analytes. The GC column used was a Supelco SPB-5 column, 15×0.32 mm with a phase thickness of 1 μm. Recoveries were calculated as an average of two trials by comparing the relative peak areas with standards that were not subjected to SM-SPE.

2.6. Biological samples

Fresh urine samples were diluted 1:1 with DI water. Sample volumes of 1.0 ml were made up by adding 10% v/v of methanol or an aqueous 30 m*M* sodium dodecyl sulfate (SDS) solution. Stock solutions containing either 1000 or 10 000 ppm bovine serum albumin were prepared in DI water; in some cases 10% v/v of an aqueous 30 m*M* SDS solution was added. Serum samples were prepared by diluting 1:2 with an aqueous 30 m*M* solution of SDS. A 10-μl aliquot of a methanol solution containing 50 ppm each of 2–3 analytes was added to each 1.0-ml sample. The final concentration of each analyte in the sample was 0.5 ppm. The samples were extracted with a 1×4 mm Silicalite disk as explained above in the single-pass procedure.

3. Results and discussion

3.1. Extraction assembly

The device used for SM-SPE (Fig. 1) must be carefully designed to provide efficient extraction and subsequent desorption on a small scale. The 1×4 mm membrane disks weigh only ~9 mg (PS–DVB)

and 11 mg (Silicalite), of which 90% is estimated to be solid particles for the extraction. The disks are rather soft and need to be supported on a thin stainless steel screen that is machined into place in the needle hub (see Section 2). It was necessary to drill out the inside of the needle hub slightly so that a conical void was created just below the membrane disk and its mesh support. This was needed to assure a smooth flow of liquid through the membrane and out the needle. Without the tapered void, the disk lay flat against the needle hub, causing the back pressure to rise and the volume of solvent needed for elution to double.

In the work described the needle containing a small membrane disk was connected to a small syringe. The aqueous sample was placed in the syringe barrel and forced manually through the needle assembly. Alternatively, air or gas pressure could be used to push through the sample.

3.2. SM-SPE of test compounds

Experimental Empore®-type membranes containing lightly sulfonated PS–DVB resins have been shown previously to effectively extract a wide variety of organic test compounds from aqueous samples [13]. Excellent recoveries were obtained with these membranes on a semi-micro scale, as indicated by the data in Table 1. The aqueous samples contained 0.17 to 1.0 ppm each of several test compounds. The average recovery for all test compounds was 97% for 1-ml samples and 95% for 6-ml samples. The relative standard deviation was 1.7%.

Table 1
SM-SPE recovery of organic compounds using a sulfonated PS–DVB resin-loaded membrane

Class	Compound	Volume of desorption solvent (μl)	Average recovery (%)	
			1-ml sample	6-ml sample
Phenol	Phenol	40	92	91
	o-Cresol	40	102	102
	2,5-Dimethylphenol40	101	98	
	2-Chlorophenol	40	100	93
	4-Chlorophenol	40	92	98
	3-Nitrophenol	40	94	93
Aldehyde	*n*-Valeraldehyde	40	88	90
	Octaldehyde	50	89	86
	Benzaldehyde	50	99	98
	Salicylaldehyde[a]	40	100	95
Alcohol	1-Pentanol[b]	20	102	95
	3-Phenyl-1-propanol[a]	20	92	91
	2-Ethyl-1-hexanol	20	94	94
	1-Octanol[b]	20	97	96
Ester	Ethyl acetoacetate	20	99	97
	Hexyl acetate	40	99	98
	Methyl benzoate	40	92	91
	Isopentyl benzoate	30	98	93
Ether	Anisole	50	98	98
Ketone	2-Pentanone	30	98	93
	4-Methyl-2-pentanone	30	100	94
	2-Hexanone[b]	30	100	100
	Acetophenone	40	99	99

[a] Eluted with methylene chloride.
[b] Eluted with ethyl acetate.
Aqueous samples contained 0.17 to 1.0 ppm of each test compound. Acetone was used for desorption of extracted compounds except where noted.

The volume of acetone required for elution varied from 20 to 50 μl. In some cases methylene chloride or ethyl acetate was used for the desorption step. With a 2-μl injection into a gas chromatograph, the fraction of the organic solvent eluate actually injected into the GC varies from about 0.1 to 0.04. In conventional SPE the fraction of eluate injected is often of the order of 0.001.

In conventional SPE an experimental Empore®-type membrane loaded with Silicalite particles has been shown to extract smaller, more polar molecules than sulfonated PS–DVB resin-loaded membranes [13]. Silicalite also extracts molecules that are somewhat larger and more hydrophobic, but bulkier compounds are excluded from the 6 Å channels in the Silicalite and are poorly extracted. Data for SM-SPE of polar test compounds with Silicalite-loaded membrane disks are presented in Table 2. The average recovery for the 29 compounds tested was 97% on 1-ml samples and 95% on 6-ml samples with a relative standard deviation of 1.9%. All of the test compounds were eluted with 40 μl of acetone.

It is known that sulfonated PS–DVB resin-loaded membranes extract larger organic compounds and the Silicalite-loaded membrane extracts small, more polar compounds. Therefore, the membranes were mixed to determine whether they can successfully extract organics in tandem from aqueous solutions. The membrane packing order did not influence the recoveries, shown in Table 3. The first analyte in

Table 2
SM-SPE recovery of organic compounds using a Silicalite-loaded membrane

Class	Compound	Average recovery (%)	
		1-ml sample	6-ml sample
Alcohol	1-Propanol	85	85
	1-Butanol	97	94
	2-Butanol	97	98
	1-Pentanol	102	99
	2-Pentanol	102	99
	1-Hexanol	101	99
	1-Octanol	99	100
	2-Octanol	101	98
	2-Ethyl-1-hexanol	93	93
	3-Ethyl-2,2-dimethyl-3-pentanol	94	94
Ester	Methyl acetate	96	95
	Ethyl acetate	97	94
	Ethyl propionate	98	96
	Ethyl butyrate	95	93
	Ethyl acetoacetate	99	96
Ketone	2-Butanone	98	96
	2-Pentanone	98	91
	4-Methyl-2-pentanone	100	97
	2-Hexanone	106	106
	3-Hexanone	98	92
	2-Heptanone	97	95
Phenol	*p*-Cresol	99	94
	4-Isopropyl phenol	97	95
Aldehyde	*trans*-Crotylaldehyde	91	89
	cis-Crotylaldehyde	96	95
	Butyraldehyde	96	92
	n-Valeraldehyde	91	88
	Hexaldehyde	97	94
	Benzaldehyde	99	97

Aqueous samples contained 0.17–1.0 ppm of each test compound. Acetone (40 μl) was used for desorption.

Table 3
SM-SPE using mixed membranes

Compound pair	Recovery (%)
Methyl acetate	91
Methyl benzoate	95
2-Butanol	99
2-Cresol	102
1-Butanol	94
3-Nitrophenol	99
Ethyl butyrate	90
2,5-Dimethylphenol	93
Ethyl acetate	90
Salicylaldehyde	90
2-Pentanone	94
2-Chlorophenol	100
Ethyl propionate	96
Phenol	93

Conditions: 0.5 mm thick sulfonated PS–DVB resin-loaded and 0.5 mm thick Silicalite-loaded membranes, single pass, 6 ml aqueous samples, 1 ml/min. Elution: 40 μl acetone, 10 s. Analyte concentration: 0.083 ppm.

each pair was selectively extracted by the Silicalite-loaded membrane and extracted little, if at all, by the sulfonated PS–DVB resin-loaded membrane. The second analyte in each pair was more favorably extracted by the sulfonated PS–DVB resin-loaded membrane. All recoveries were about 90% or greater with a relative standard deviation of 2.3%. These results show that the membranes perform just as well in tandem as they do alone. This technique promises to expand the scope of organic compounds that are amenable to solid-phase extraction.

3.3. Extraction of biological samples

Extraction and quantification of organic compounds from biological samples such as urine and serum present several specific problems. Biological samples contain components such as proteins, lipids, saccharides and salts in varying concentrations. The organic compounds to be extracted range in polarity and may associate with the matrix components. Human urine has been found to contain several hundred volatile organic compounds [14]. These organic volatiles consist of certain essential nutrients, intermediates, waste products, environmental contaminants and other substances of low molecular mass involved in metabolism. Most of these volatiles are also present in serum [15].

Fresh urine, bovine serum albumin and human serum samples were analyzed to determine the extraction ability of SM-SPE for samples of this type. Compounds previously identified in human urine [15,16] and serum [15,17,18] were added to the samples in low concentrations. A Silicalite-loaded membrane was used for these experiments for two reasons. One was that the analytes selected were more successfully extracted by Silicalite than by sulfonated PS–DVB resins. The other reason was that preliminary experiments showed that large biological compounds do not clog up the pores of Silicalite.

Results of these SM-SPE experiments are summarized in Table 4. Diluted urine samples required the addition of 10% v/v of methanol or, better, addition of 10% v/v of an aqueous 30 m*M* sodium dodecylsulfate (SDS) solution to reduce the back pressure. SDS binds to proteinaceous material and releases protein-bound drugs, etc. [19,20]. As a result, proteins are not adsorbed onto the membrane and thus do not interfere with the SPE process. The chromatograms of eluates from samples treated with SDS were much cleaner than those containing methanol. The average recovery of 20 compounds from SDS-treated urine samples was 88% with a relative standard deviation (R.S.D.) of 3%.

SM-SPE experiments were performed with 1000 and 10 000 ppm samples of bovine serum albumin. No noticeable changes in back pressure were observed on sampling 1000 ppm albumin samples. The average recovery of 17 test compounds was 94% (Table 4) with a relative standard deviation of 2%. However, sampling 10 000 ppm albumin required the addition of 10% v/v of an aqueous 30 m*M* SDS solution to prevent a serious increase in back pressure. Recovery of test compounds with added SDS averaged 88% with a R.S.D. of 2%.

Serum samples required dilution (1:2) using an aqueous 30 m*M* solution of SDS. The serum samples were more viscous than the aqueous-albumin samples and contained more potential interferences. After many extractions with the same membrane, the back pressure did not increase, implying no fouling of the membrane by protein adsorption. The average

Table 4
Recoveries of test compounds from various biological samples using a Silicalite-loaded membrane

Compound	Recovery (%)			
	Urine, SDS	H_2O, 1000 ppm albumin	H_2O, 1000 ppm albumin, SDS	Serum, SDS
1-Butanol	95	98	97	90
2-Butanol	–	102	96	87
1-Pentanol	89	99	95	101
2-Pentanol	91	–	–	–
1-Hexanol	–	101	100	101
2-Ethyl-1-Hexanol	–	96	92	93
1-Octanol	93	91	93	100
2-Octanol	–	91	93	100
2-Butanone	100	101	101	100
2-Pentanone	100	101	100	100
4-Methyl-2-Pentanone	97	100	95	88
2-Hexanone	100	93	100	99
3-Hexanone	88	–	–	–
2-Heptanone	94	98	90	100
2-Methylbutyraldehyde	59	–	–	–
n-Valeraldehyde	–	88	87	90
trans-2-Pentenal	93	–	–	–
Hexaldehyde	–	95	92	97
Benzaldehyde	99	97	94	97
Thiophene[a]	81	–	–	–
R-Carvone	92	–	–	–
Benzene	78	82	75	55
Toluene	65	79	67	76
Phenol[a]	88	–	–	–
p-Cresol	100	–	–	–
Chloroform	58	75	58	68

[a] Extracted with a sulfonated resin-loaded membrane.

recovery of 18 test compounds was 91% with a R.S.D. of 2%.

3.4. Double pass sampling

A convenient manual technique for SM-SPE is to draw the sample via the needle tip up through the membrane. The sample is then pushed back through the membrane a second time and expelled out the needle. This double-pass technique should ensure a high degree of extraction. It is particularly convenient for field sampling; elution of the analytes immobilized on the membrane can be completed in the laboratory if desired.

Minor adjustments in the membrane-needle assembly were required for the double-pass technique to be practical. A second mesh screen was inserted above the membrane to hold it in place during the sample-draw step. Sampling was slow during the draw step due to the resistance of flow of 1-mm thick membranes. This problem was avoided by reducing the membrane thickness to 0.5 mm or in some cases to 0.33 mm.

Recovery data are given in Table 5 for samples extracted by a 0.5×4 mm sulfonated PS–DVB resin-loaded membrane using double-pass sampling. The sampling time for a 1-ml aqueous sample was only 45–60 s (draw time 30–45 s; push time 15 s). The average recovery for sample compounds was 89% with a R.S.D. of 2%. Recovery data for double-pass extractions using a 0.33×4 mm Silicalite-loaded membrane are given in Table 6. In this case the sampling time was 50–85 s (draw, 30–45 s; push 20–30 s). The average recovery for sample compounds was 99% with a R.S.D. of 2%.

The amount of sorbent particles in these thinner

Table 5
Recovery of test compounds using a sulfonated PS–DVB resin-loaded membrane (0.5 mm thick) and double-pass sampling

Class	Compound	Recovery (%)
Phenol	*o*-Cresol	60
	2,5-Dimethylphenol	76
	4-Chlorophenol	68
Aldehyde	Octylaldehyde	100
	Benzaldehyde	95
	Salicylaldehyde	100
Alcohol	3-Phenyl-1-propanol	85
	2-Ethyl-1-hexanol	93
	1-Octanol	99
Ester	Hexyl acetate	100
	Methyl benzoate	94
	Isopentyl benzoate	100
Ether	Anisole	81
Ketone	2-Hexanone	82
	2-Heptanone	100

Conditions: 1.0-ml aqueous samples containing 0.5 ppm of each test compound. Draw time 30–45 s, push time 15 s. Elution with 20–50 μl acetone in 5–10 s.

Table 6
Recovery of test compounds using a Silicalite-loaded membrane (0.33 mm thick) and double-pass sampling

Class	Compound	Recovery (%)
Alcohol	1-Butanol	86
	1-Pentanol	100
	2-Pentanol	93
	1-Hexanol	103
	2-Ethyl-1-hexanol	95
	1-Octanol	101
	2-Octanol	103
Aldehyde	*n*-Valeraldehyde	102
	Hexaldehyde	99
	Benzaldehyde	100
Ketone	2-Butanone	92
	2-Pentanone	103
	4-Methyl-2-pentanone	102
	2-Hexanone	103
	3-Hexanone	99
	2-Heptanone	100
Ester	Ethyl propionate	102
	Ethyl butyrate	101

Conditions: 1-ml aqueous samples, 0.5 ppm of each test compound. Sampling times; draw 30–45 s, push 20–30 s. Elution with 40 μl acetone, 10 s.

membranes is quite small: 4.5 mg for 0.5×4 mm sulfonated PS–DVB and ~3.7 mg for 0.33×4 mm Silicalite. However, the analyte in a 1.0-ml sample containing 1 ppm is smaller yet: ~1 μg. With such small amounts of solid-extractant particles in the membranes it is useful to know the effect of analyte concentration in the sample on its percentage recovery in SM-SPE. Recoveries of 2-hexanone by double-pass SM-SPE with a 0.33×4 mm Silicalite-loaded membrane were as follows: 0.005 ppm, 91%; 0.01 ppm, 96%; 0.10 ppm, 103%; 1.0 ppm, 106%; 10 ppm, 84%; 100 ppm, 81%. Thus, recoveries >90% were obtained for 2-hexanone concentrations ranging from 0.005 to 1.0 ppm. Some overloading and, therefore, lower recoveries occurred at 10 and 100 ppm. Recoveries of 2-hexanone on the 0.5×4 mm PS–DVB resin-loaded membrane were lower: 0.005 ppm, 67%; 0.01 ppm, 70%; 0.10 ppm, 72%; 1.0 ppm, 79%; 10 ppm, 67%; 100 ppm, 54%.

4. Conclusions

Two basic approaches can be used for solid-phase extraction of solutes from liquid samples. In "conventional" SPE the liquid sample is passed through a mini-column or membrane containing the solid extractive particles. Extraction of the solutes tends to be rapid and essentially complete. A second approach is illustrated by SPME in which a fiber coated with the solid-phase extractant is placed in the sample liquid. An equilibrium is attained in which a fixed portion of each solute is taken up by the fiber. Often only a small fraction of each solute is actually extracted. However, all of the solutes on the fiber are thermally desorbed into a gas chromatograph for further analysis.

Semi-micro SPE retains many of the best aspects of both of these basic approaches. SM-SPE is a total extraction technique but the sample size has been reduced to 1–6 ml and the volume of eluting solvent to only 20–50 μl. This in turn reduced the amount of waste produced and lowered the time needed per run. SM-SPE also provides flexibility in sampling and extraction design. Two types of sampling techniques were used, single and double pass. Also, membrane disks of different compositions were mixed to achieve a multimodal extraction, which is difficult to

accomplish in conventional SPE. Finally, the SM-SPE device could be brought on-site to perform extractions immediately, saving transport time and storage space. The extracted compounds could be eluted immediately or the needle hubs could be stored in air-tight containers for later elution.

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