Capillary GC Column Choices for Residual Solvent Analyses

Using Direct Injection or Solid Phase Microextraction (SPME)

Supelco®
Analytical Products

In the process of preparing a pharmaceutical product, you can potentially retain residual organic solvents in the final preparation. In the interest of safety for the patient, the trend has been to use less toxic solvents during the manufacture of pharmaceutical preparations. Residual solvent analysis is therefore an important step in pharmaceutical quality control, and your choice of capillary GC column will affect these results.

We present the results of using the traditional direct injection technique, as well as, the fast, solvent free, and economical technique of SPME.

In the United States, the regulations require that you examine most pharmaceuticals to confirm the absence or very limited presence of many solvents. Current guidelines published by the International Conference on Harmonization of Technical Re- quirements for Registration of Pharmaceuticals for Human Use (ICH) describes a list of specific solvents, along with daily expo- sure limits. (1) The guidelines classify these solvents based on their toxicity:

- Class I: Solvents to be avoided
- Class II: Solvents to be limited
- Class III: Solvents with low toxic potential
- Solvents for which no adequate toxicological data is available

The compound lists for Classes I, II, and III contain 61 different solvents. No single column is capable of separating them all. For this reason, both of the analytical methods outlined by the United States and European Pharmacopoeia (USP and EP) describe the use of several capillary columns of different chemistries (2,3). We compared three columns that are equivalent to those described in both the EP and USP methods for the analysis of 60 of the 61 solvents (those detectable by GC/FID). **Table 1** outlines the descriptions of these columns.

We analyzed the solvents by direct injection as three separate mixtures, divided by their individual classes (I, II or III). We prepared these standards specifically for this application. They are available through our Custom Chemical Standards Program. We can tailor these standards in combinations and concentrations to meet your specific needs. The run conditions were the same for all three columns. As expected, the elution order of the solvents varied for each column. The different elution orders are due to differences in chemical and physical properties of the solvents (boiling points, polarizability, dipole moments, number of hydrogen donor and hydrogen acceptor sites) and the strengths of the stationary phase-analyte interactions as described in **Tables 2 and 3**. The type and strength of these interactions determines the amount of time you will retain the analyte on the column.

Table 1. USP and EP Column Designations and Supelco Equivalents

Method	Column Designation	Supelco® Equivalent
USP <467>, Method I	G27	Equity®-5, cat. 28279-U and precolumn, cat. 25339
USP <467>, Methods IV&V	G43	OVI-G43, cat. 25396 and precolumn cat. 25339
USP <467>, Method VI	Various	Includes SUPELCOWAX® 10, cat. 25301-U
EP Method 2.4.24 - Primary column	6% polycyanopropyl phenylsiloxane	OVI-G43, cat. # 25396
EP Method 2.4.24 – Secondary column	Macrogol 20000	SUPELCOWAX® 10, cat.# 25301-U

Table 2. Stationary Phase–Analyte Interactions

Interaction Type	Effect on Selectivity
Dispersive	elution by boiling point
π-π	elution by number of π-bonds
Dipole-induced dipole	elution by polarizability, elution by dipole moment
Dipole-dipole	elution by dipole moment
Hydrogen bonding	elution by number of H-bond donor and/or acceptor sites

Table 3. Stationary Phase–Residual Solvent Interactions

Column	Type of Interaction
Equity®-5	dispersive dipole-induced dipole π–π
OVI-G43	dispersive dipole-induced dipole dipole-dipole π–π
SUPELCOWAX® 10	dispersive H-bonding dipole-dipole

We show chromatograms of each class of solvents on the three columns (**Figures A through C**) and information on the identity, retention time, and concentration of each peak (**Tables 4 through 6**). The advantage of having multiple columns with different selectivity, becomes evident when examining the information in these tables. A coelution on the primary analytical column will often be resolved on a secondary or confirmation column. For example, ethyl ether and ethanol, which coeluted on the OVI-G43, were resolved on both the Equity®-5 and SUPELCOWAX® 10 columns. Under the run conditions used, a dual column analysis on the Equity®-5 and SUPELCOWAX® 10 columns will resolve all 60 solvents. Pairs not resolved on the OVI-G43 will be resolved on either the SUPELCOWAX® 10 or the Equity®-5 columns. Since the run conditions were kept the same for all three columns, this makes it possible to do a single analysis of a solvent mixture by running two columns at the same time in a single GC oven. We suggest having all three columns available in your laboratory. The most suitable primary column for a particular analysis can be selected by studying **Tables 4 through 6** and **Figures A through C**. Likewise, a second column can be chosen that will provide valuable confirmation information. This will guarantee success in being able to analyze any combination of solvents from the ICH list.

Table 4. Retention Times and Elution Order of Class I Residual Solvents on the Equity®-5, SUPELCOWAX® 10 and OVI-G43 Columns

Peak	Identification	Concentration (µg/mL)	Equity®-5 Retention Time	SUPELCOWAX® 10 Retention Time	OVI-G43 Retention Time
1	1,1-Dichloroethylene	4000	7.35	2.97	7.21
2	1,1,1-Trichloroethane	5000	18.11	5.54	17.35
3	1,2-Dichloroethane	2500	18.29	17.55	19.22
4	Carbon tetrachloride	2000	19.50	5.54	18.12
5	Benzene	1000	19.50	7.78	19.06

Table 5. Retention Times and Elution Order of Class II Residual Solvents on the Equity®-5, SUPELCOWAX® 10 and OVI-G43 Columns

Peak	Identification	Concentration (µg/mL)	Equity®-5 Retention Time	SUPELCOWAX® 10 Retention Time	OVI-G43 Retention Time
1	Methanol	1000	3.54	6.04	4.56
2	Acetonitrile	1000	5.91	11.80	8.30
3	Methylene chloride	1000	8.06	7.60	8.84
4	Nitromethane	250	9.94	22.91	NI
5	Hexane	1000	12.98	2.24	11.08
6	cis-1,2-Dichloroethylene	1000	14.00	10.97	14.74
7	Chloroform	300	15.16	13.28	16.67
8	2-Methoxyethanol	250	16.54	23.59	19.38
9	1,2-Dimethoxyethane	500	18.79	7.06	19.38
10	Cyclohexane	1000	19.56	2.87	17.54
11	Ethylene glycol	1000	20.62	36.92	29.44
12	Formamide	1000	20.62	40.49	29.90
13	Trichloroethylene	400	22.27	10.97	21.73
14	1,4-Dioxane	1000	22.69	16.31	23.13
15	2-Ethoxyethanol	800	22.89	25.37	24.47
16	Methylcyclohexane	1000	23.92	3.30	22.34
17	Pyridine	1000	24.91	23.59	25.80
18	Toluene	1000	26.44	14.28	26.12
19	Dimethylformamide	1000	26.75	28.99	29.73
20	Methyl butyl ketone	250	27.33	18.01	28.32
21	Chlorobenzene	1000	30.48	25.15	30.35
22	Dimethylacetamide	1000	31.01	31.24	33.76*
23	m-Xylene	333	31.41	21.75	31.08
24	p-Xylene	333	31.41	21.41	31.08
25	o-Xylene	333	32.46	23.83	32.21
26	n-Methylpyrrolidone	5000	37.73	38.07	39.93
27	Tetralin	500	42.33	34.70	41.98
28	Sulfolane	800	43.34	49.53	46.53

NI: not integrated, *coelutes w/solvent

Table 6. Retention Times and Elution Order of Class III Residual Solvents on the Equity®-5, SUPELCOWAX® 10 and OVI-G43 Columns

Peak	Identification	Concentration (µg/mL)	Equity®-5 Retention Time	SUPELCOWAX® 10 Retention Time	OVI-G43 Retention Time
1	Ethanol	3000	4.90	7.56	6.29
2	Acetone	3000	6.04	4.06	6.58
3	2-Propanol	3000	6.23	7.26	7.92
4	Pentane	3000	6.23	2.06	5.99
5	Ethyl ether	3000	6.64	2.32	6.29
6	Ethyl formate	3000	7.16	7.06	7.39
7	Methyl acetate	3000	7.78	4.31	8.54
8	1-Propanol	3000	9.50	14.76	12.60
9	Methyl-t-butyl ether	3000	10.33	2.65	9.92
10	Acetic acid	3000	NI	33.02	21.53
11	2-Butanone	3000	12.57	6.14	15.01
12	sec-Butanol	3000	13.07	13.45	16.47
13	Ethyl acetate	3000	14.68	5.78	15.58
14	Tetrahydrofuran	3000	16.21	4.93	16.35
15	iso-Butanol	3000	16.21	19.23	19.39
16	n-Butanol	3000	19.48	22.19	22.02
17	Isopropyl acetate	3000	19.48	6.14	19.89
18	Heptane	3000	22.20	2.65	20.47
19	Propyl acetate	3000	23.11	9.71	23.52
20	Isoamyl alcohol	3000	24.33	24.91	26.16
21	4-Methyl-2-pentanone	3000	24.68	11.62	25.72
22	n-Amyl alcohol	3000	26.13	26.49	27.73
23	Isobutyl acetate	3000	26.54	12.34	26.84
24	Butyl acetate	3000	28.51	17.72	28.79
25	Dimethyl sulfoxide	3000	29.18	35.51	33.02
26	Anisole	3000	33.30	29.65	33.54
27	Cumene	3000	33.68	23.38	33.29

NI: not integrated

Figure A. Class I Solvents on the Equity®-5, SUPELCOWAX ®10 and OVI-G43

Solvents - Pharmaceutical Solvents, Class 1 (GC)

Oven	35 °C, hold 15 min., 5 °C/min to 200 °C
Inj.	225 °C
Det.	FID, 250 °C
Flow	30 cm/sec (constant) He at 35 °C
Inject.	1 µL, 33:1 split
Liner	single taper
Sample	Class I: 1000-5000 ppm In DMSO

Class 1 Solvents on Equity®-5 column

Column	30 m x 0.5 3mm ID, 5.0 µm w/5 m intermediate polarity guard
Cat. No.	**28279-U**

Class 1 Solvents on SUPELCOWAX® 10 column

Column	30 m x 0.53 mm ID, 1.0 µm
Cat. No.	**25301-U**

Class 1 Solvents on OVI-G43 column

Column	30 m x 0.53 mm ID x 3.0 µm w/5 m intermediate polarity guard
Cat. No.	**25396**

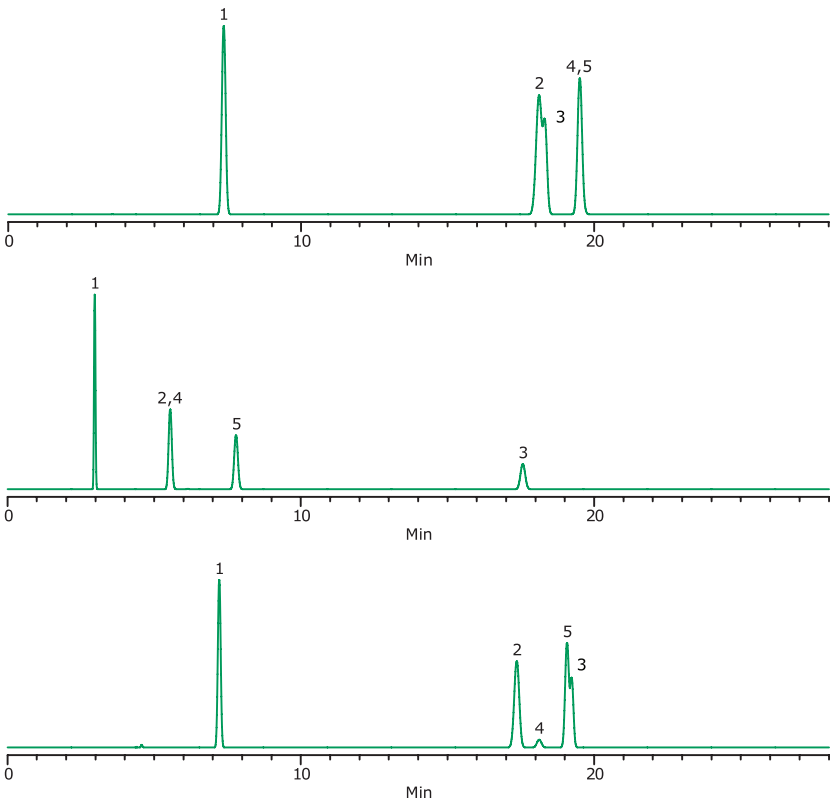


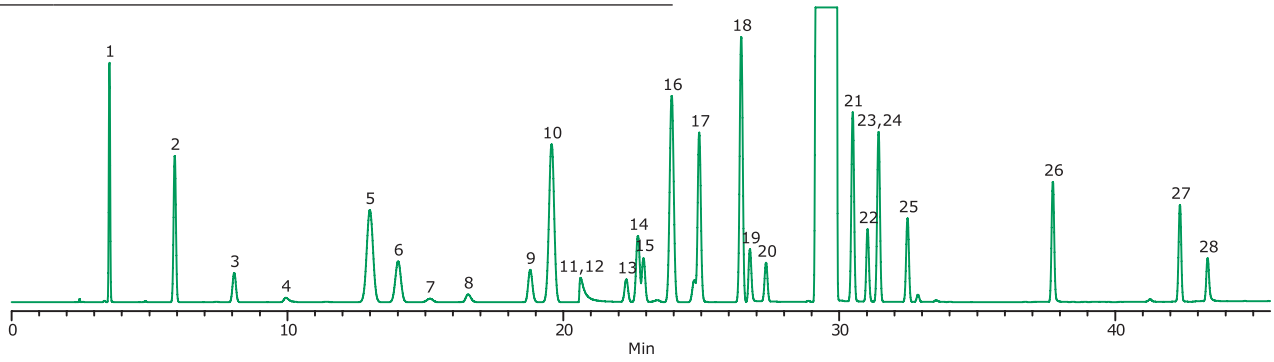
Figure B. Class II Solvents on the Equity®-5, SUPELCOWAX® 10 and OVI-G43 columns

Solvents - Pharmaceutical Solvents, Class 2 (GC)

Oven	35 °C, hold 15 min., 5 °C/min to 200 °C
Inj.	225 °C
Det.	FID, 250 °C
Flow	30 cm/sec (constant) He at 35 °C
Inject.	1 µL, 33:1 split
Liner	single taper
Sample	Class II and n-methylpyrrolidone, 250-1000 ppm in DMSO

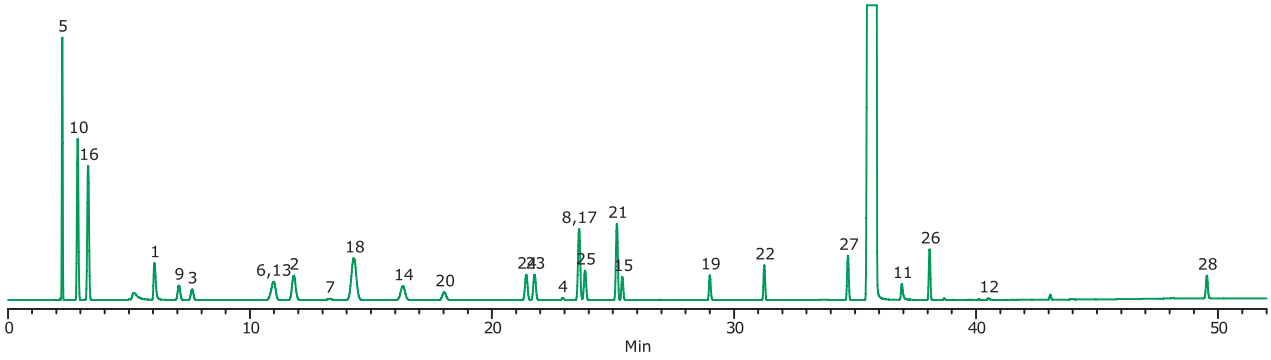
Class 2 Solvents on Equity®-5 column

Column	30 m x 0.53 mm ID, 5.0 µm w/5 m intermediate polarity guard
Cat. No.	**28279-U**



Class 2 Solvents on SUPELCOWAX® 10 column

Column	30 m x 0.53 mm ID, 1.0 µm
Cat. No.	**25301-U**



Class 2 Solvents on OVI-G43 column

Column	30 m x 0.53 mm ID x 3.0 µm w/5m intermediate polarity guard
Cat. No.	**25396**

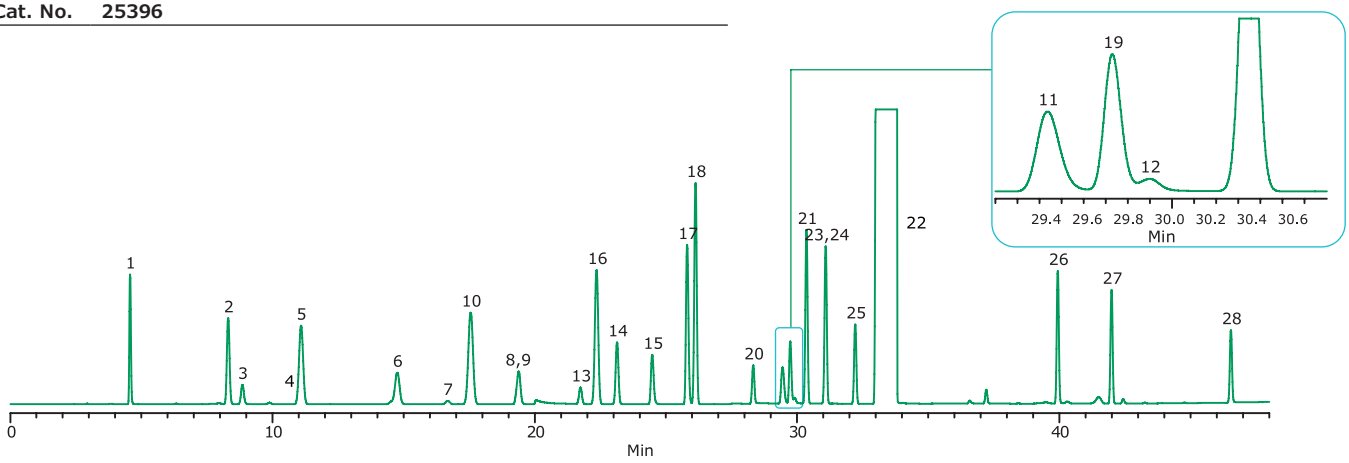


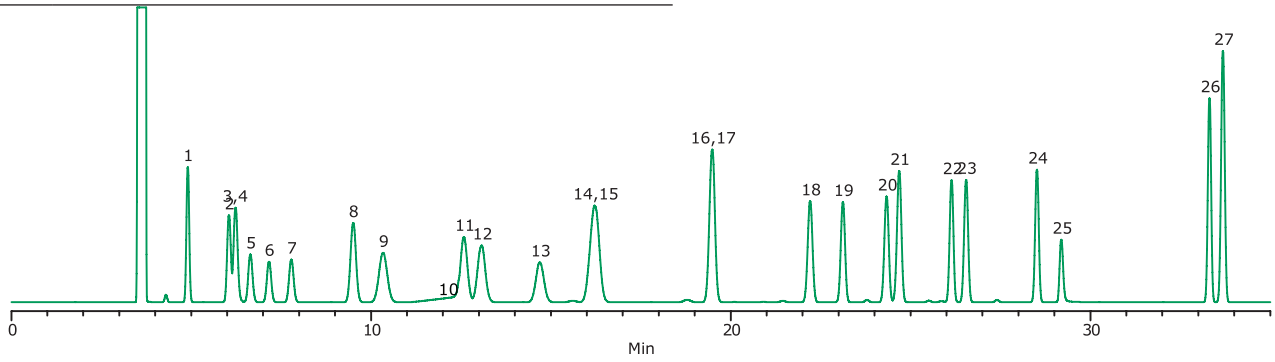
Figure C. Class III Solvents on the Equity®-5, SUPELCOWAX® 10 and OVI-G43

Solvents - Pharmaceutical Solvents, Class 3 (GC)

Oven	35 °C, hold 15 min., 5 °C/min to 200 °C
Inj.	225 °C
Det.	FID, 250 °C
Flow	30 cm/sec (constant) He at 35 °C
Inject.	1 µL, 33:1 split
Liner	single taper
Sample	Class III: approx. 3000 ppm in MeOH

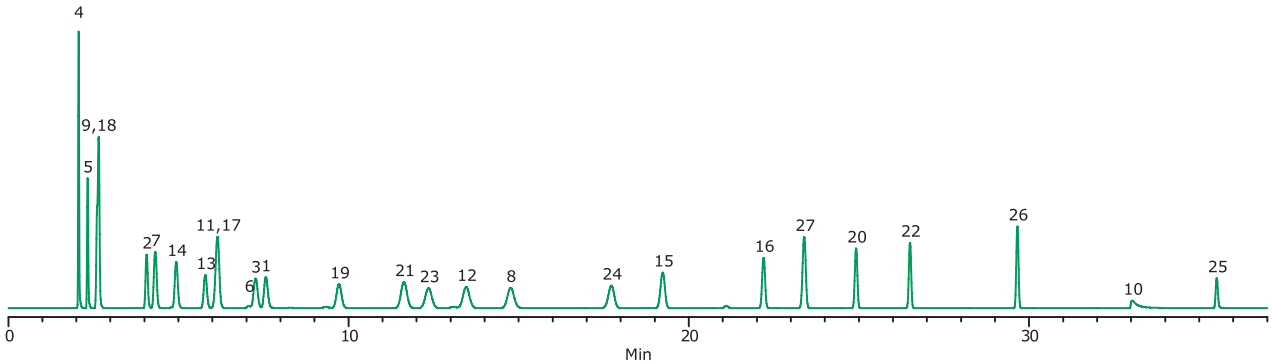
Class 3 Solvents on Equity®-5 column

Column	30 m x 0.53 mm ID, 5.0 µm w/5 m intermediate polarity guard
Cat. No.	**28279-U**



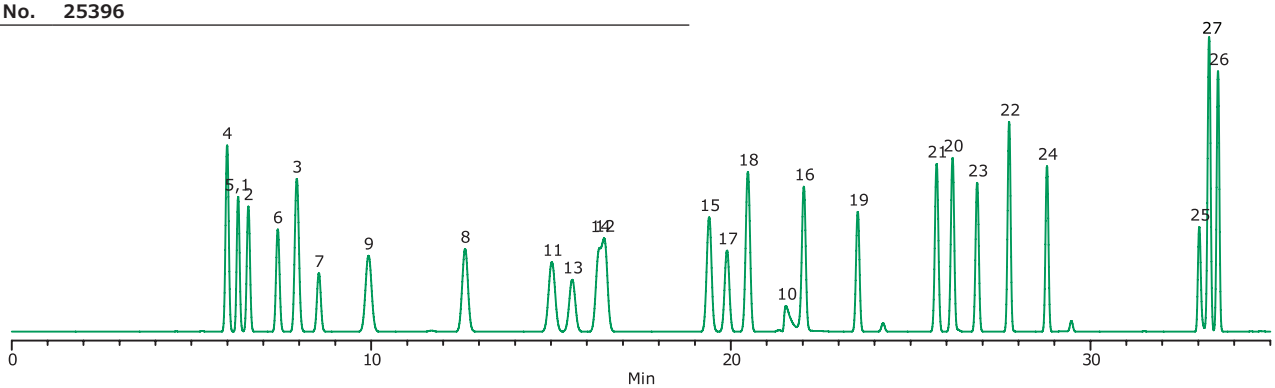
Class 3 Solvents on SUPELCOWAX® 10 column

Column	30 m x 0.53 mm ID, 1.0 µm
Cat. No.	**25301-U**



Class 3 Solvents on OVI-G43 column

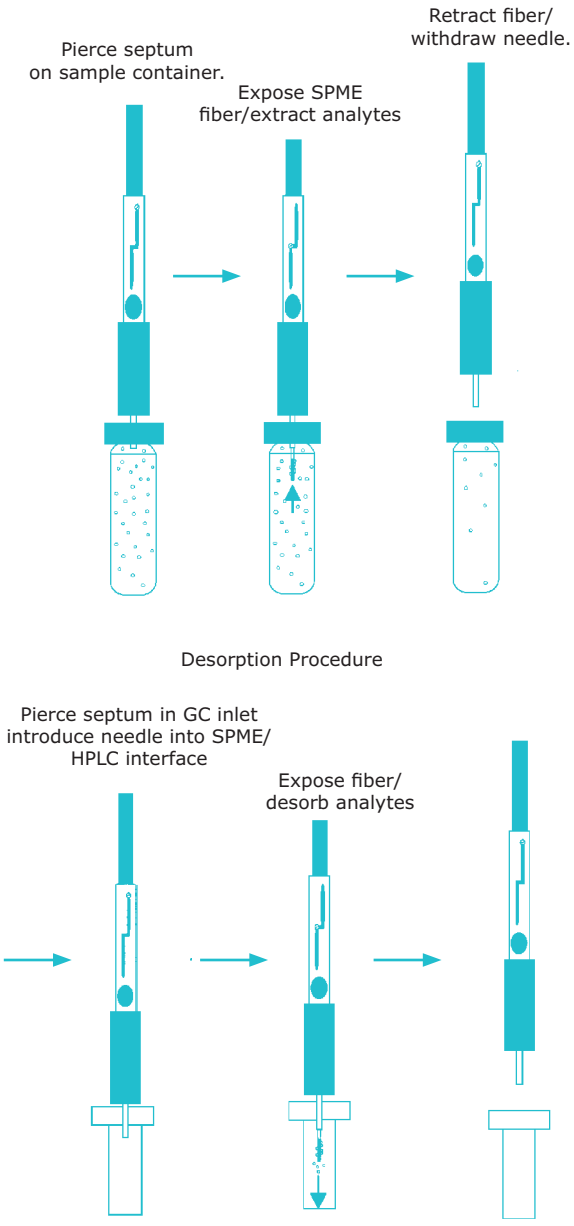
Column	30 m x 0.53 mm ID x 3.0 µm w/5m intermediate polarity guard
Cat. No.	**25396**



Fast GC Analysis of Residual Solvents using SPME with Dual Capillary GC Columns

The analysis of residual solvents can be time consuming and not always effective. As shown in the previous section, cycle time for the GC analysis of residual solvents is about 45 minutes. This analysis time is long if multiple samples need to be evaluated daily. Typically, analysts use either a static headspace method or direct injection of the sample for quantifying residual solvents. Both of these methods require long, high capacity columns. When these columns are used, analysis times can range from 30 to 60 minutes depending on the analytes you monitor. The method described below uses short narrow bore columns coupled with SPME. This technique provides the resolution you need with analysis times of less than 10 minutes.

Figure D. Solid Phase Microextraction



SPME is an excellent alternative to headspace analyzers and direct injections. With SPME, you insert a coated fiber into the headspace of the vial and the analytes are concentrated onto the fiber. After a given amount of time (usually 5 min) the fiber is retracted into a needle, removed from the vial and inserted into the GC injection port where the fiber is desorbed (See **Figure D**). The fiber immediately releases the analytes into the injection port and onto the analytical column.

A low volume liner increases linear velocity and delivers the analytes onto the column with little or no band broadening. Therefore, you can use narrow bore columns. Since narrow bore columns provide more plates per meter than larger bore columns, you can use shorter length columns. This greatly reduces the analysis time while providing resolution similar to longer columns.

As previously mentioned, no single column is capable of separating a complex mixture of analytes classified as residual solvents; therefore, a second column is required. In this procedure, we installed a nonpolar Equity®-1 column and an intermediate polarity VOCOL® column in one injection port. These columns provide distinct differences in polarity while having compatible temperature ranges. We matched the column flows by shortening the column with the longer methane retention time. When the methane retention times between the two columns were within 10% of each other, the columns were ready for separating analytes.

For the evaluation of SPME and dual column separations, we prepared the solvents by class and extracted them from water using SPME. We determined that water was the best solvent choice for extraction of the solvents. However, if the drug or finished product is not water-soluble, you can dissolve it in a solvent such as DMSO and spike it into a water sample containing

Table 7. Residual Solvent Extraction and Analysis Conditions

Extraction Conditions for Class I	
Fiber	100 µm PDMS
Sample	1 ppm each analyte in 2 mL water with 25% NaCl
Extraction	heated headspace, 50 °C for 5 min in 4 mL vial
Desorption	3 min at 250 °C
Extraction Conditions for Class II	
Fiber	85 µm Polyacrylate
Sample	5 ppm each analyte in 2 mL water & 25% NaCl, pH 11
Extraction	heated headspace, 60 °C for 5 min in 4 mL vial
Desorption	3 min at 250 °C
Extraction Conditions for Class III	
Fiber	100 µm PDMS
Sample	5 ppm each analyte in 2 mL water & 25% NaCl, pH 2
Extraction	heated headspace, 60 °C for 5 min in 4 mL
Desorption	3 min at 250 °C
GC Conditions	
Columns	Equity®-1 and VOCOL® both 10 m x 0.20 mm ID x 1.2 µm
Oven	40 °C (hold 0.75 min) to 200 °C at 20 °C/min (hold 10 min)
Carrier Gas	helium, 35 cm/sec @40 °C (9 psi constant pressure)
Injection Port	Split 5:1@40°C, 0.75 mm liner, 2 columns in 1 port using 0.8 mm graphite ferrule
Detector	FID

25% sodium chloride. When extracting polar solvents, it is best to add salt to the sample. You can add the salt after you dissolve the sample and you can adjust the pH to enhance extraction efficiency.

Table 7 shows the best conditions for extracting the analytes in each class. We were able to extract most analytes at concentrations of 5 ppm or less using these conditions.

We extracted the analytes using heated headspace from an aqueous matrix containing 25% salt. We recommend two types of fiber coatings. The 100 µm PDMS fiber is suitable for Class I and Class III solvents. Many analytes in the Class II list require a more polar fiber for extraction, we therefore selected the 85 µm polyacrylate fiber. **Figures E** through J show the chromatograms of the analytes extracted by SPME.

Figure E. Class I Solvents on Equity®-1 Column Using SPME (1 ppm each in water)

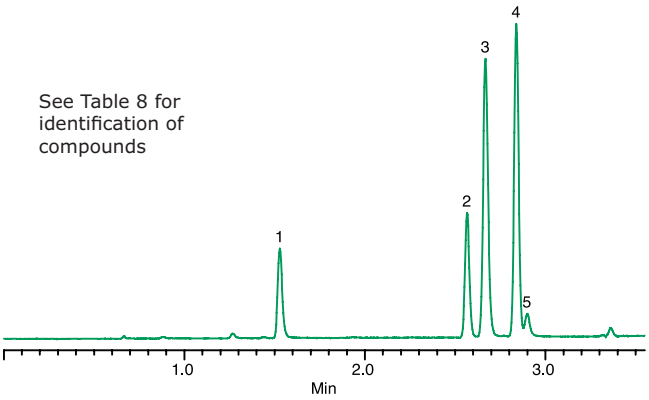


Figure F. Class I Solvents on VOCOL® Column Using SPME (1 ppm each in water)

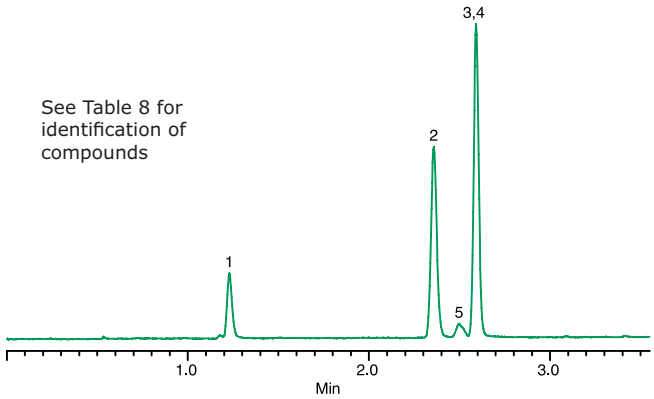


Figure G. Class II Solvents on Equity®-1 Column Using SPME (5 ppm each in water)

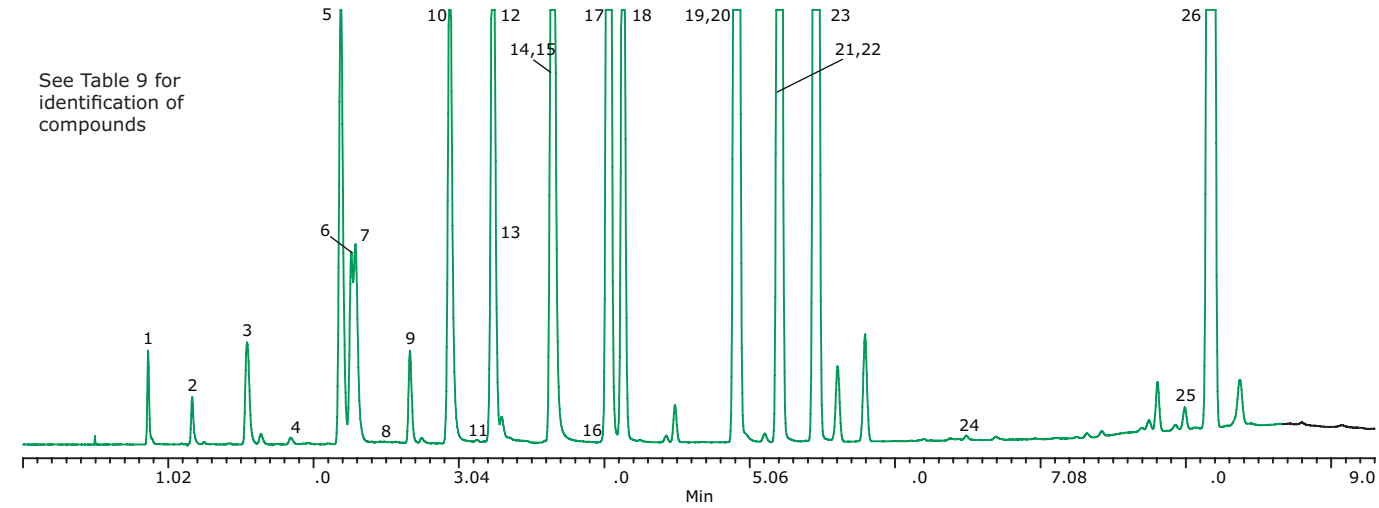


Figure H. Class II Solvents on VOCOL® Column Using SPME (5 ppm each in water)

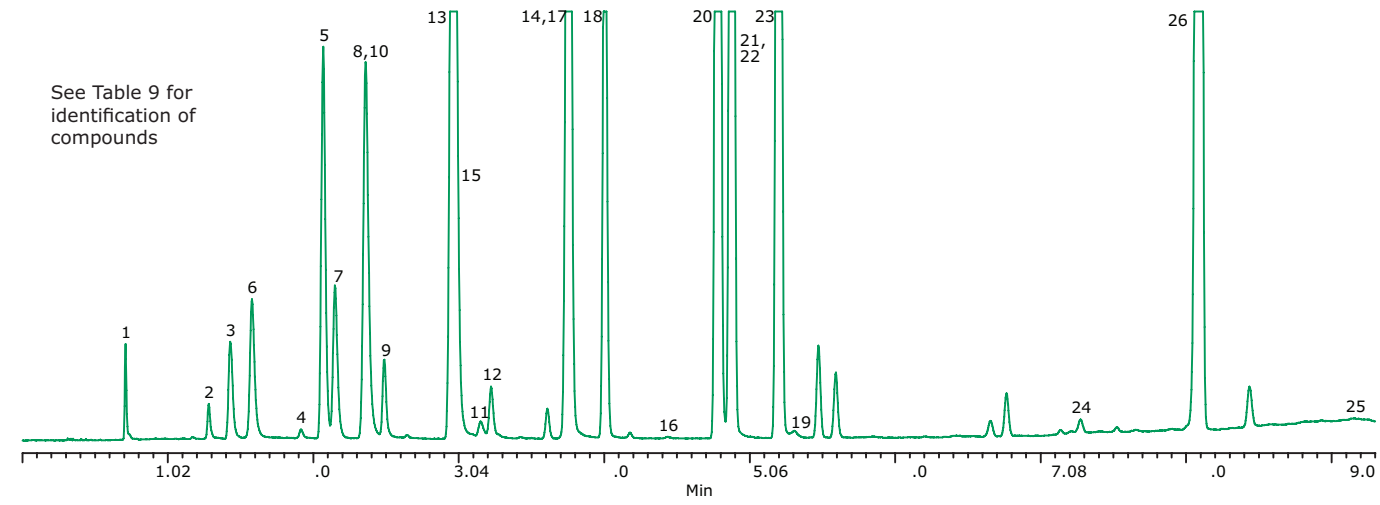


Figure I. Class III Solvents on Equity®-1 Column using SPME (5 ppm each in water)

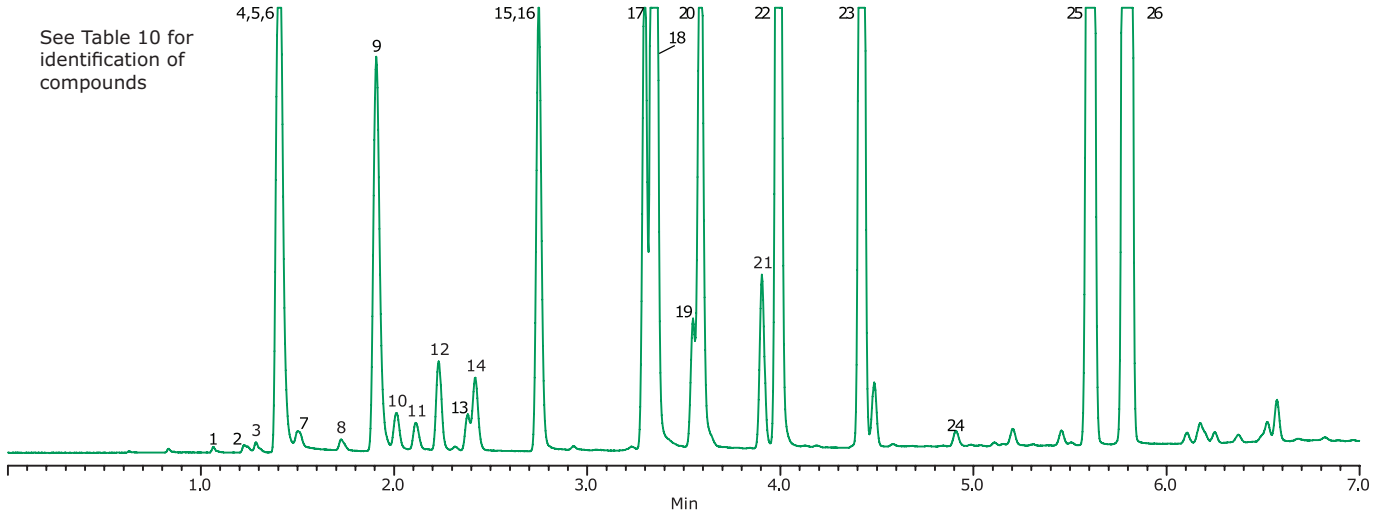
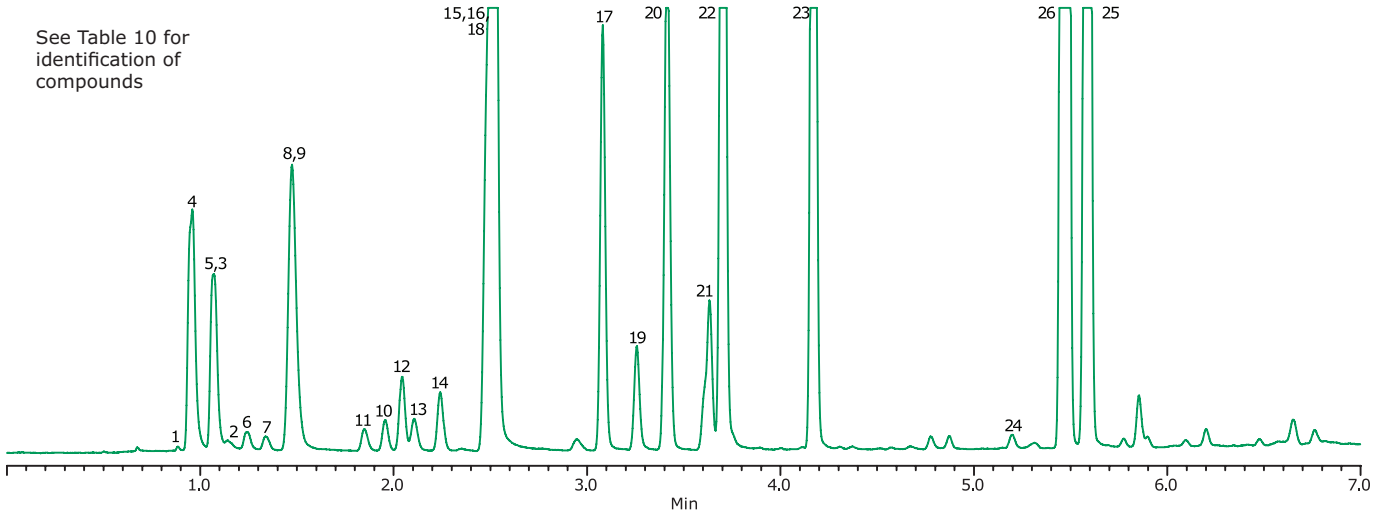


Figure J. Class III Solvents on VOCOL® Column using SPME (5 ppm each in water)



SPME is excellent for extracting nonpolar and moderately polar analytes. Only polar analytes with low vapor pressures are difficult to extract. Some of the peaks look very small, but that is in comparison to some nonpolar analytes that you can easily extract. By reducing the intensity scale, one can see that the peaks are sufficiently large and symmetrical for proper quantification.

Some of the solvents such as ethylene glycol and formamide have very low vapor pressures and you cannot analyze these by headspace. Therefore, we have not shown these in the chromatograms. Other aprotic and polar solvents such as dimethylacetamide, DMSO, sulfolane, n,n-dimethylformamide and glycol ethers are difficult to analyze by headspace. You can use SPME to extract these analytes, but the minimum quantitation limits will be higher than for less polar analytes. You usually analyze these analytes by direct injection due to their low vapor pressures. By immersing the SPME fiber directly into the aqueous matrix, you can achieve slightly lower detection limits relative to headspace SPME.

Tables 8 through 10 show a listing of all of the analytes in the various classes along with the concentration that we used during the SPME evaluation. In the tables, we make a recommendation to the applicability of SPME for detection and quantification of the analytes. R is for recommended by SPME, D is for difficult by SPME, and N is for not recommended by SPME. We base these recommendations on a minimum quantitation limit of 5 ppm or less. In cases where D is listed, it would be difficult to quantify the analyte at the concentration listed, but at higher concentration levels, these compounds should be quantifiable using SPME.

Table 8. Class I Solvents Using SPME

Peak	Identification	Concentration (µg/mL)	SPME Use	Equity®-1 Retention Time	VOCOL® Retention Time
1	1,1-Dichloroethene	1	R	1.54	1.32
2	1,1,1-Trichloroethane	1	R	2.58	2.36
3	1,2-Dichloroethane	1	R	2.66	2.63
4	Benzene	1	R	2.82	2.63
5	Carbon tetrachloride	1	R	2.89	2.51

R=recommended; D=difficult; N=not recommended

Table 9. Class II Solvents Using SPME

Peak	Identification	Concentration (µg/mL)	SPME Use	Equity®-1 Retention Time	VOCOL® Retention Time
1	Methanol	5	R	0.87	0.69
2	Acetonitrile	5	R	1.17	1.26
3	Methylene chloride	5	R	1.52	1.56
4	Nitromethane	5	R	1.64	1.89
5	Hexane	5	R	2.26	2.04
6	cis-1,2-Dichloroethylene	5	R	2.18	2.12
7	Chloroform	5	R	2.34	2.35
8	2-Methoxyethanol	5	D	2.43	2.30
9	1,2-Dimethoxyethane	5	R	2.66	2.54
10	Cyclohexane	5	R	2.94	2.36
11	2-Ethoxyethanol	5	D	3.30	3.12
12	1,4-Dioxane	5	R	2.97	3.21
13	Trichloroethene	5	R	3.23	2.85
14	Pyridine	5	R	3.62	3.77
15	Methylcyclohexane	5	R	3.66	2.98
16	Dimethylformamide	5	D	3.87	4.39
17	Toluene	5	R	4.03	3.77
18	Methyl butyl ketone	5	R	4.14	4.02
19	Dimethylacetamide	5	D	4.88	5.60
20	Chlorobenzene	5	R	4.92	4.81
21	p-Xylene	5	R	5.21	4.20
22	m-Xylene	5	R	5.21	4.20
23	o-Xylene	5	R	5.46	5.24
24	n-Methylpyrrolidone	5	D	6.66	7.25
25	Sulfolane	5	D	8.14	9.12
26	Tetralin	5	R	8.18	8.14
	Ethylene glycol	1000	N		
	Formamide	1000	N		

R=recommended; D=difficult; N=not recommended

Table 10. Class III Solvents using SPME

Peak	Identification	Concentration (µg/mL)	SPME Use	Equity®-1 Retention Time	VOCOL® Retention Time
1	Ethanol	5	R	1.10	0.92
2	Acetone	5	R	1.25	1.15
3	2-Propanol	5	R	1.32	1.07
4	Pentane	5	R	1.39	0.96
5	Ethyl ether	5	R	1.41	1.07
6	Methyl acetate	5	R	1.52	1.34
7	Ethyl formate	5	R	1.43	1.24
8	1-Propanol	5	R	1.75	1.52
9	Methyl-t-butyl ether	5	R	1.92	1.47
10	2-Butanone	5	R	2.03	1.96
11	sec-Butanol	5	R	2.13	1.84
	Acetic acid	5	D	2.18	1.73
12	Ethyl acetate	5	R	2.25	2.04
13	Tetrahydrofuran	5	R	2.39	2.24
14	iso-Butanol	5	R	2.43	2.11
15	n-Butanol	5	R	2.75	2.49
16	Isopropyl acetate	5	R	2.76	2.50
17	Propyl acetate	5	R	3.31	3.09
18	Heptane	5	R	3.35	2.52
19	Isoamyl alcohol	5	R	3.56	3.28
20	4-Methyl-2-pentanone	5	R	3.60	3.43
21	n-Amyl alcohol	5	R	3.91	3.64
22	Isobutyl acetate	5	R	3.99	3.69
23	Butyl acetate	5	R	4.43	4.19
24	Dimethyl sulfoxide	5	D	4.90	5.20
25	Anisole	5	R	5.61	5.63
26	Cumene	5	R	5.80	5.51

R=recommended; D=difficult; N=not recommended

We determined that 57 of 60 analytes can be analyzed by SPME, with eight of these being somewhat difficult to extract at 5 ppm. SPME is a good alternative to conventional headspace analysis because of the short analysis time and good recovery for the majority of the residual solvent analytes.

Using SPME for Quantitative Analysis of Residual Solvents

Many pharmaceutical companies use SPME on a routine basis for residual solvent analyses. They have demonstrated reproducible and quantitative results using SPME. The work of Scypinski and Smith at Hoffmann-La Roche Inc. (Nutley, New Jersey, USA) demonstrated the use of SPME for quantitative analysis of residual solvents. Their work compared headspace SPME and immersion SPME for determining residual solvents in several water-soluble drug substances (4).

Immersion and headspace SPME were essentially equal with respect to precision, sensitivity, and accuracy (**Table 11**). The Hoffmann-La Roche chemists preferred the headspace method because it prolonged the lifetime of the SPME fiber. A 100 µm polydimethylsiloxane-coated fiber provided higher sensitivity toward the nonpolar analytes (i.e., the residual solvents). A polyacrylate-coated fiber offered higher sensitivity toward the polar analytes (alcohols). Using the polydimethylsiloxane-coated fiber, detection limits ranged from 0.06 µg/mL and 0.3 µg/mL for 1,4-dioxane (by headspace and immersion, respectively) to 0.002 µg/ mL for benzene (both techniques). For their analysis, they added methanol at 1.0% v/v in the water diluent to obtain reproducible residual solvent results. Based on these results, the chemists concluded that the SPME sample introduction technique is useful for screening residual solvents in pharmaceutical drug substances.

Because liquid and headspace sampling methods differ in kinetics, you should consider the two approaches complementary. For a given sampling time, other analysts have found immersion SPME is more sensitive than headspace SPME for analytes predominantly present in the liquid (5). The reverse was true for analytes that reside primarily in the headspace. These generalizations can be used to your advantage to selectively adsorb more volatile or less volatile compounds, as a situation warrants. For higher sensitivity from headspace SPME, the sample headspace should be as small as is practical. Zhang and Pawliszyn present a detailed theoretical discussion of headspace SPME in reference 6.

SPME is fast, easy, economical, and eliminates the costs and hazards associated with using organic solvents. Under consistent sampling conditions, you can extract analytes with good precision over wide ranges of concentrations. Good precision also makes the technique effective in quantitative analyses. If you are interested in reducing the time and expense of sample concentration in your analyses, SPME is the ideal answer to your needs.

Table 11. Precision and Detection Limits of SPME/Capillary GC for Organic Volatile Impurities and Final Recrystallization Solvent

	Precision (% RSD)		Detection Limit (µg/mL)	
	Headspace	Immersion	Headspace	Immersion
Acetone	1.1	0.5	0.2	0.4
Ethanol	7.0	5.8	5.0	2.0
Isopropanol	1.4	1.9	0.6	1.6
Benzene	2.7	2.8	0.002	0.002
Chloroform	3.2	2.2	0.03	0.04
1,4-Dioxane	1.9	2.2	0.06	0.3
Methylene chloride	2.6	2.2	0.06	0.08
Trichloroethene	3.4	3.2	0.02	0.01

Data from reference 4.

References

1. ICH Guidance for Industry, Q3C Impurities: Residual Solvents, US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), ICH December 1997.
2. USP 25, NF20, <467>, pgs. 1943-1944.
3. European Pharmacopoeia 4, 2.4.24, pgs. 96-100.
4. Rosen Shaw, S., A. M. Smith, L. Clark Nelson, and S. Scypinski, poster presentation, American Association of Pharmaceutical Science Conference, June 1994.
5. Yang, X. and T. Peppard, J. Agric. Food Chem. 42: 1925-1930 (1994).
6. Zhang, Z. and J. Pawliszyn, Anal. Chem. 65: 1843-1852 (1993). References not available from Supelco.

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