Application Note 62

Monitor Organic Volatile Impurities (OVIs) in Pharmaceutical Products, Using Solid Phase Microextraction/Capillary GC

A 100µm polydimethylsiloxane-coated SPME fiber provided higher sensitivity for less polar analytes (i.e., organic volatile impurities) and a polyacrylate-coated fiber provided higher sensitivity for polar analytes (alcohols). Using the polydimethylsiloxane-coated fiber, SPME/GC detection limits ranged from 0.06µg/mL and 0.3µg/mL for 1,4-dioxane (headspace and immersion sampling, respectively) to 0.002µg/mL for benzene (both sampling techniques).

Key Words:
- organic volatile impurities • OVIs • solvents
- pharmaceuticals • pharmaceutical quality
- solid phase microextraction

Solid phase microextraction – SPME▲ – is a simple, solventless extraction procedure in which a phase-coated fused silica fiber is immersed in a liquid sample or exposed to the headspace above a liquid or solid sample. Analytes adsorb to the phase, and then are thermally desorbed in the injection port of a gas chromatograph and transferred to a capillary column. Selectivity can be altered by changing the phase type or thickness according to the characteristics of the analytes. For example, the small distribution constants and low polarity of chlorinated and aromatic volatile organic compounds in environmental samples dictate the use of a thick, nonpolar phase for efficient extraction. Analyte recovery can be improved, or selectivity altered in favor of more volatile or less volatile compounds, by agitating the sample, adding salt, changing the pH, sampling the headspace rather than the sample (or vice versa), or making other changes in conditions.

Chemists at Hoffmann-La Roche Inc. (Nutley, New Jersey, USA) compared headspace SPME and immersion SPME for determining organic volatile impurities (OVIs) and residual solvents in several water-soluble drug substances (1). The United States Pharmacopoeia (USP) chapter <467> describes several methods of analysis for OVIs (benzene, chloroform, 1,4-dioxane, methylene chloride, trichloroethylene) in pharmaceutical drug substances and raw materials. In addition, pharmaceutical manufacturers must monitor residual organic solvents from the manufacturing process of a bulk drug substance.

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

Table 1. Precision and Detection Limits of SPME/Capillary GC for Organic Volatile Impurities and Final Recrystallization Solvents

	Precision (% RSD)		Detection Limit (µg/mL)	
Solvent	Headspace SPME	Immersion SPME	Headspace SPME	Immersion SPME
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
Trichloro-ethylene	3.4	3.2	0.02	0.01

Data from reference 1.

Because liquid and headspace sampling methods differ in kinetics, the two approaches can be considered complementary. For a given sampling time, other analysts found immersion SPME was more sensitive than headspace SPME for analytes predominantly present in the liquid (2). The reverse was true for analytes that were primarily present in the liquid (2). The reverse was true for analytes that were primarily in the headspace. These generalizations can be used to 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. A detailed theoretical discussion of headspace SPME is presented in reference 3.

Figure A. Residual Organic Solvents in a Pharmaceutical Preparation

SPME: **100µm polydimethylsiloxane phase fiber**
Cat. No. : **57300-U**
headspace or immersion sampling (15 min)
1 min desorption

Column: **6% cyanopropylphenyl / 94% polydimethylsiloxane phase, 75m x 0.53mm ID, 3.0µm film**
Oven: 40°C (35 min) to 220°C at 40°C/min, hold 5 min
Carrier: helium, 35cm/sec
Det.: FID, 80°C
Inj.: splitless (closed 3 min), 200°C

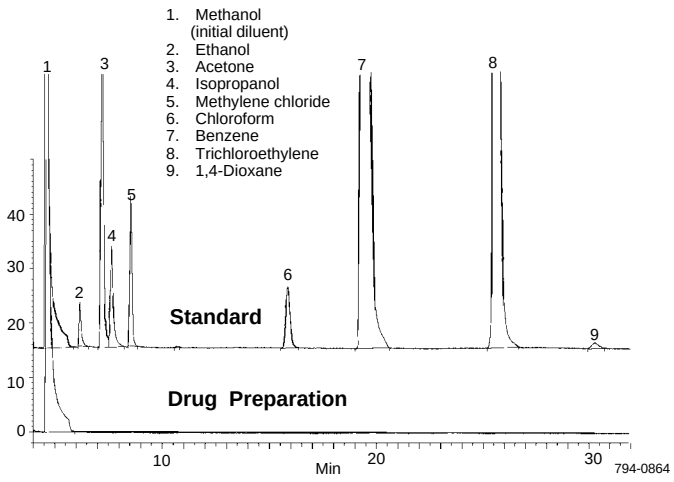

Figure courtesy of Stephen Scypinski, Ann-Marie Smith, Linda Clark Nelson, and Sandra Rosen Shaw, Hoffmann-La Roche, Nutley, NJ, USA.

SPME is fast, easy, and economical, and eliminates the costs and hazards associated with using organic solvents. Under consistent sampling conditions, analytes can be extracted with good precision over wide ranges of concentrations. SPME can be used for screening samples prior to a detailed analysis. 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 might be the ideal answer to your needs.

Contact our Technical Service Department for expert answers to your questions (phone 800-359-3041 or 814-359-3041, FAX 800-359-3044 or 814-359-5468).

Ordering Information:

Description	Cat. No.
SPME Fiber Holder	
Initially you must order both holder and fiber assembly. Holder is reusable indefinitely.	
For manual sampling	**57330-U**
For Varian 8100/8200 autosampler requires Varian SPME upgrade kit	**57331**

SPME Fiber Assemblies (pkg. of 3)

polydimethylsiloxane coating	100µm	30µm	7µm
For manual sampling	**57300-U**	**57308**	**57302**
For Varian 8100/8200 autosampler	**57301**	**57309**	**57303**

85µm polyacrylate coating	
For manual sampling	**57304**
For Varian 8100/8200 autosampler	**57305**

SPME Fiber Assortment Kit

One fiber assembly each:
100µm polydimethylsiloxane (best for volatile analytes),
7µm polydimethylsiloxane (for nonpolar–intermediate polarity semivolatiles),
85µm polyacrylate (for polar semivolatiles)

For manual sampling	**57306**
For Varian 8100/8200 autosampler	**57307**

Capillary GC Column

OVI-G43 (cyanopropylphenyl/polydimethylsiloxane)
75m x 0.53mm ID, 3.0µm film — available on request

▲Solid phase microextraction technology is licensed exclusively to Supelco (US patent pending; European patent #0523092).

References

1. Rosen Shaw, S., A.-M. Smith, L. Clark Nelson, and S. Scypinski, poster presentation, American Association of Pharmaceutical Science Conference, June 1994.
2. Yang, X. and T. Peppard, J. Agric. Food Chem., 42: 1925-1930 (1994).
3. Zhang, Z. and J. Pawliszyn, Anal. Chem. 65: 1843-1852 (1993).

References not available from Supelco.

Acknowledgments

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For additional SPME fibers and fiber kits, and for SPME accessories, please refer to our current catalog.

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