Application Note 70

Organic Volatile Impurities in Pharmaceutical Products: Selectivity of Capillary GC Columns

Methods for separating and quantifying organic volatile impurities (OVIs) – residual solvents potentially present in pharmaceutical preparations – are described by the US Pharmacopoeia in USP <467>. The two polysiloxane-phase columns described in USP <467> (e.g., SPB-5 and OVI-G43) effectively separate the five regulated OVIs plus many other residual solvents. However, a column with a bonded polyethylene glycol stationary phase (SUPELCOWAX 10) offers a different elution pattern for separating these analytes, making it the best column for confirming results.

Key Words:
• organic volatile impurities • solvents • SUPELCOWAX 10

In the process of preparing a pharmaceutical product, residual organic solvents potentially can be retained in the final preparation. In the United States, most pharmaceutical products must be examined to confirm the absence or very limited presence of benzene, chloroform, 1,4-dioxane, methylene chloride, or trichloroethylene. These solvents, referred to as organic volatile impurities (OVIs), have been determined to be toxic. Methods for separating and quantifying the five regulated OVIs are described by the US Pharmacopoeia in USP <467> (1). Two additional solvents, acetonitrile and pyridine, are proposed for regulation by the European Pharmacopoeia. In addition to the regulated OVIs, other residual organic solvents from the final recrystallization step (e.g., acetone, ethanol, isopropanol) also could be present in a pharmaceutical product.

We compared the two polysiloxane-phase columns listed in USP <467> (G27 and G43), plus a polyethylene glycol-phase column (Table 1), for separating the five regulated OVIs and other common residual solvents. As expected, the elution order of these solvents varies for each stationary phase, according to differences in chemical and physical properties of the solvents

Table 1. Columns Used to Monitor OVIs

Column Type*	Bonded Phase	Phase Thickness
SPB™-5 (USP G27)	5% phenyl 95% methylpolysiloxane	5.0µm
OVI-G43 (USP G43)	6% cyanopropylphenyl 94% dimethylpolysiloxane	3.0µm
SUPELCOWAX™10 (USP G16)	polyethylene glycol	1.0µm

*All 30m x 0.53mm ID.

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
SPB-5	dispersive dipole-induced dipole π-π
OVI-G43	dispersive dipole-induced dipole dipole-dipole π-π
SUPELCOWAX 10	dispersive H-bonding dipole-dipole

(boiling points, polarizability, dipole moments, number of hydrogen donor and hydrogen acceptor sites) and consequent strengths of the stationary phase-analyte interactions (Tables 2 and 3). The type and strength of each temporary interaction determines the amount of time the analyte is retained on the column.

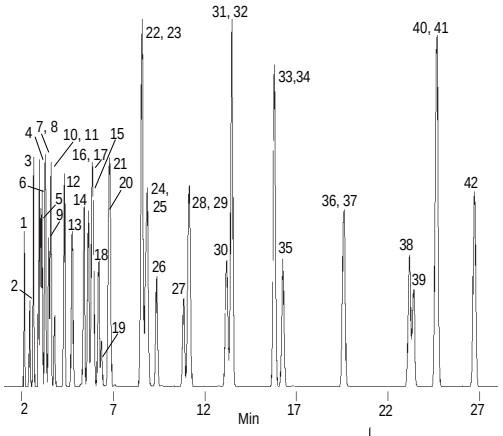
Figure A shows typical elution orders for 42 common solvents from the three columns. The elution order was similar, but not identical, for the two polysiloxane stationary phases, SPB-5 and OVI-G43. The polyethylene glycol phase, SUPELCOWAX 10, provided the largest number of changes in elution order and resolution (Table 4 and Figure A), making it the best choice when you want to use a second column to confirm results.

These results indicate that, as expected, either the SPB-5 or OVI-G43 column will enable you to effectively monitor any or all of the seven OVIs specified in USP <467> or by the European Pharmacopoeia. Among 42 common solvents, however, there are several coelutions and partial resolutions on either of these columns, or on a SUPELCOWAX 10 column. The most suitable column for a particular analysis can be selected by studying Table 4 and Figure A. Alternatively, a dual-column analysis on an OVI-G43 column and a SUPELCOWAX 10 column will resolve all 42 solvents and provide valuable confirmational information.

Figure A. Common Solvents Used in Pharmaceutical Processing

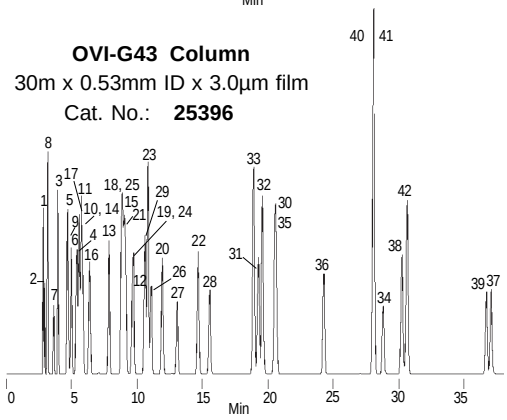
Col. Temp.: 40°C (5 min) to 200°C at 2°C/min
Carrier: helium, 35cm/sec (at 40°C)
Det.: FID, 250°C
Inj.: 0.2µL of neat solvents mix
split (100:1), 250°C

SPB-5 Column
30m x 0.53mm ID x 5.0µm film
Cat. No.: **25347**



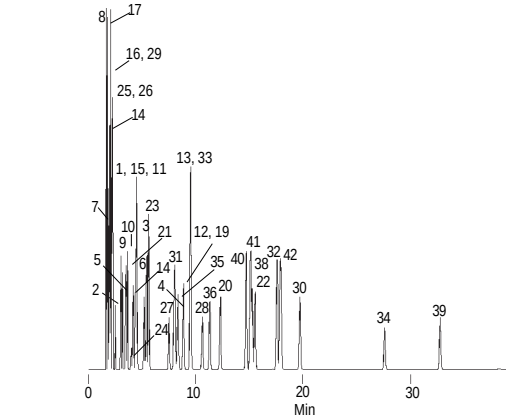
1. Methanol
2. Methyl formate
3. Ethanol
4. Acetonitrile
5. Acetone
6. Isopropanol
7. Ethyl ether
8. Pentane
9. Ethyl formate
10. Methylene chloride ($MeCl_2$)
11. t-Butanol
12. 2-Butanol
13. n-Propanol
14. Methyl t-butyl ether (MTBE)

OVI-G43 Column
30m x 0.53mm ID x 3.0µm film
Cat. No.: **25396**



15. Methyl ethyl ketone (MEK)
16. Isopropyl ether
17. Hexane
18. Ethyl acetate
19. Chloroform
20. Isobutanol
21. Tetrahydrofuran (THF)
22. 1-Butanol
23. Benzene
24. Carbon tetrachloride
25. Cyclohexane
26. Diethoxymethane
27. Trichloroethylene
28. 1,4-Dioxane
29. Heptane
30. Isopentanol
31. Methyl isobutyl ketone (MIBK)

SUPELCOWAX 10 Column
30m x 0.53mm ID x 1.0µm film
Cat. No.: **25301-U**



32. Pyridine
33. Toluene
34. Dimethylformamide
35. Isobutyl acetate
36. n-Butyl acetate
37. Dimethylsulfoxide (DMSO)
38. Methyl isoamyl ketone (MIAK)
39. Dimethylacetamide (DMA)
40. p-Xylene
41. m-Xylene
42. o-Xylene

794-0611, 0613, 0612

Table 4. Elution Order for 23 Common Residual Solvents

SPB-5	OVI-G43	SUPELCOWAX 10
Methanol	Methanol	Hexane
Ethanol	Ethyl ether	Ethyl ether
Acetonitrile**	Ethanol	MTBE
Acetone	Acetone	Heptane
Isopropanol	Isopropanol	Acetone
Ethyl ether	$MeCl_2$*	$MeCl_2$*
$MeCl_2$*	MTBE	Tetrahydrofuran
t-Butanol	Hexane	Ethyl acetate
2-Butanol	t-Butanol	MEK
MTBE	Acetonitrile**	Methanol
MEK	Ethyl acetate	t-Butanol
Hexane	MEK	Isopropanol
Ethyl acetate	Tetrahydrofuran	Ethanol
Chloroform*	Chloroform*	Benzene*
Tetrahydrofuran	2-Butanol	Trichloroethylene*
1-Butanol	Heptane	Acetonitrile**
Benzene*	Benzene*	MIBK
Trichloroethylene*	Trichloroethylene*	2-Butanol
1,4-Dioxane*	1-Butanol	Chloroform*
Heptane	1,4-Dioxane*	Toluene
MIBK	Toluene	1,4-Dioxane*
Pyridine**	MIBK	1-Butanol
Toluene	Pyridine**	Pyridine**

Column Polarity: Mean value for 5 McReynolds constants = 62 (SPB-5), 101 (OVI-G43), 437 (SUPELCOWAX 10)
*OVIs, regulated by USP <467>
**Proposed for regulation in European Pharmacopoeia method
Shading designates coelution

Ordering Information:

Capillary GC Columns

SPB-5 (USP G27) 30m x 0.53mm ID, 5.0µm film	**25347**
OVI-G43 (USP G43) 30m x 0.53mm ID, 3.0µm film	**25396**
SUPELCOWAX 10 (USP G16) 30m x 0.53mm ID, 1.0µm film	**25301-U**

Reference

1. USP 23 – NF18 The United States Pharmacopoeia - The National Formulary, USP Convention, Rockville, Maryland, 1995, USP <467>, p1746-1748.

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