Study of Residual Solvents in Various Matrices by Static Headspace

Application Note

Abstract

United States Pharmacopeia (USP) chapter <467> is a widely used method for identifying and quantifying Organic Volatile Impurities (OVI) used in the production of pharmaceuticals. Many of these OVIs, also known as residual solvents, are known or potential carcinogens and must be monitored due to the risks they pose to consumers and the environment. For this study, VOC data will be presented for a variety of matrices using static headspace and GC/FID, following the guidelines of USP <467>.

Introduction

USP Chapter <467>, Residual Solvents, allows pharmaceutical companies the option to use numerous GC and headspace parameters to determine residual solvents in their pharmaceutical products. One of these parameters is the carrier gas type, helium or nitrogen, for the GC and headspace system. Nitrogen is a lower cost alternative to helium. This study will evaluate the use of helium and nitrogen as the headspace and GC carrier gas for USP <467> for Class 1, 2A and 2B solvents.

The van Deemter equation for gas chromatography[1] indicates that nitrogen has a different optimal linear velocity than helium. This study will evaluate GC linear velocities of 35cm/sec and 25cm/sec for nitrogen, to determine any potential effects on the USP residual solvents assay.

The method precision will be evaluated following the FDA Guidance for Industry Bioanalytical Method Validation document[2]. This document recommends a minimum of five determinations and a coefficient of variation (CV) of less than 15%. Seven standards at the USP concentration will be prepared for this study.

Experimental-Instrument Conditions

A Teledyne Tekmar Versa Automated Headspace Vial Sampler was connected to a GC with FID for this study. A 624 column, 30m x 0.32mm x 1.8µm was used to meet the USP<467> G43 column requirement. The GC carrier gas linear velocity is set to 35cm/sec for both helium and nitrogen. The GC carrier gas linear velocity was also set to 25cm/sec for nitrogen based on the van Deemter equation.

Both gases were evaluated on the Versa and GC/FID in various combinations of helium and/or nitrogen. The different gas and flow combinations for each experiment are shown in Table 1. The Versa parameters for this set of experiments are listed in Table 2. The GC/FID parameters are listed in Table 3.

	Carrier Gas		Linear Velocity (cm/sec)	GC Liner Dimension (mm, inside)
Experiment	Versa	GC/FID		
1	Helium	Helium	35	1
2	Nitrogen	Nitrogen	35	1
3	Nitrogen	Nitrogen	25	1
4	Nitrogen	Nitrogen	25	3.5
5	Nitrogen	Helium	35	3.5

Table 1: Different Gas and Flow Combinations for the USP<467> Gas Experiments

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Versa Headspace Instrument Parameters			
Variable	**Value**	**Variable**	**Value**
GC Cycle Time	65.00min	Pressurize	11psig
Valve Oven Temp	85 °C	Pressurize Time	2.00min
Transfer Line Temp	85 °C	Pressurize Equil Time	0.25min
Platen/Sample Temp	80 °C	Loop Fill Pressure	9psig
Platen Temp Equil Time	0.50min	Loop Fill Time	2.00min
Sample Equil Time	60.00min	Inject Time	0.25min
Mixer	Off		

Table 2: Versa Parameters

GC/FID Parameters	
USP G43 Column	624, 30m, 0.32mm ID, 1.8µm; Linear Velocity 35cm/sec for Helium and Nitrogen, 25cm/sec for Nitrogen
Oven Program	40 °C for 20min; 10 °C/min to 240 °C, hold for 20min, run time 60min
Inlet:	Temperature 140 °C, Helium or Nitrogen Carrier Gas, Purge Flow 3.0mL/min
FID	250 °C, Hydrogen Flow 40.0mL/min, Air Flow 400.0mL/min, Makeup Flow 30mL/min

Table 3: GC/FID Parameters

Standard Sample Preparation

This study used Class 1, Class 2A and Class 2B USP residual solvent standards obtained from Restek. Dimethylsulfoxide (DMSO) was obtained from Sigma-Aldrich and was 99.5% grade.

Class 1, Class 2A and Class 2B standard stock solutions were prepared following the USP <467> procedure. 1.0mL of the Class 1 or 2A was transferred to 20mL headspace vials containing 5mL of water. 5.0mL of Class 2B was transferred to 20mL headspace vials containing 1.0mL of water. The blank sample vial contained 6.0mL of water.

Results

All of the peak area data was evaluated to calculate the averages and CV's. The chromatography system passes USP <467> requirements when the signal-to-noise (S/N) ratio of 1,1,1-trichloroethane in the Class 1 standard solution is not less than 5, the S/N ratio of the other peaks in the Class 1 standard is not less than 3, and the resolution between acetonitrile and methylene chloride is not less than 1.0.

Table 4 shows the CV data for the Class 1 compounds for the different experiments. Table 5 shows the signal to noise data for the Class 1 compounds for the different experiments. An example chromatogram for a Class 1 standard can be found in Figure 1.

Table 6 presents the CV data for the Class 2A compounds for the five different experiments. Table 7 shows the S/N data for the Class 2A compounds for the different experiments. An example chromatogram for a Class 2A standard can be found in Figure 2. Table 8 presents the coefficient of variation data for the Class 2B compounds for the different experiments. An example chromatogram for a Class 2B standard can be found in Figure 3.

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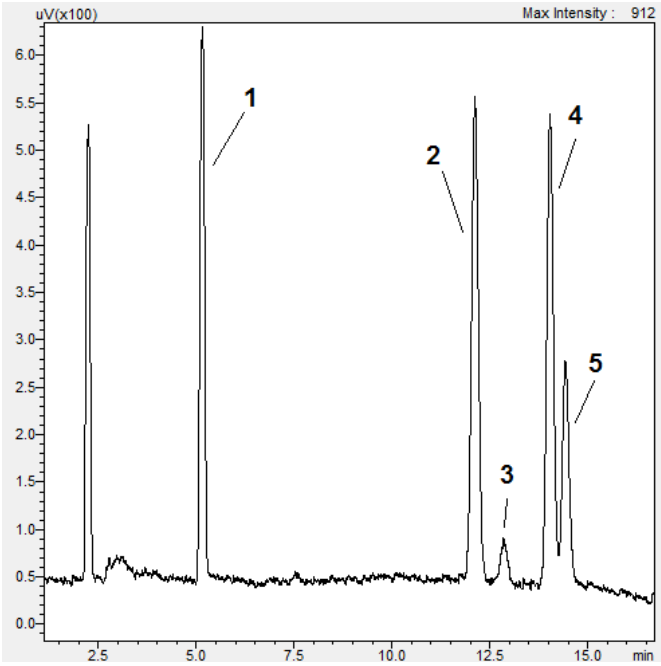

Figure 1: Chromatogram of a Class 1 Standard (data for corresponding peaks can be found in Tables 4 and 5)

Class 1 Compound	Conc (ppm)	CV (n=6) for Gas Experiments				
		1	2	3	4	5
1,1-Dichloroethene[1]	0.07	0.99	5.73	2.29	2.74	2.12
1,1,1-Trichloroethane[2]	0.08	1.45	4.80	2.32	2.76	1.35
Carbon Tetrachloride[3]	0.03	2.08	6.80	4.72	2.75	2.61
Benzene[4]	0.02	1.49	5.02	2.35	3.54	2.02
1,2-Dichloroethane[5]	0.04	1.72	7.28	5.28	4.05	2.72

Table 4: Coefficient of Variation (CV) for Class 1 Compounds with a G43 USP<467> Gas Chromatography Column

Class 1 Compound	Conc (ppm)	S/N ratio for Gas Experiments				
		1	2	3	4	5
1,1-Dichloroethene	0.07	99.79	93.62	57.47	52.05	80.42
1,1,1-Trichloroethane	0.08	80.11	68.36	57.53	45.32	70.20
Carbon Tetrachloride	0.03	7.71	6.61	5.30	3.86	6.07
Benzene	0.02	68.35	55.19	55.28	45.94	73.53
1,2-Dichloroethane	0.04	27.16	21.66	27.98	22.61	34.42

Table 5: Signal to Noise Ratio (S/N) for Class 1 Compounds with a G43 USP<467> Gas Chromatography Column

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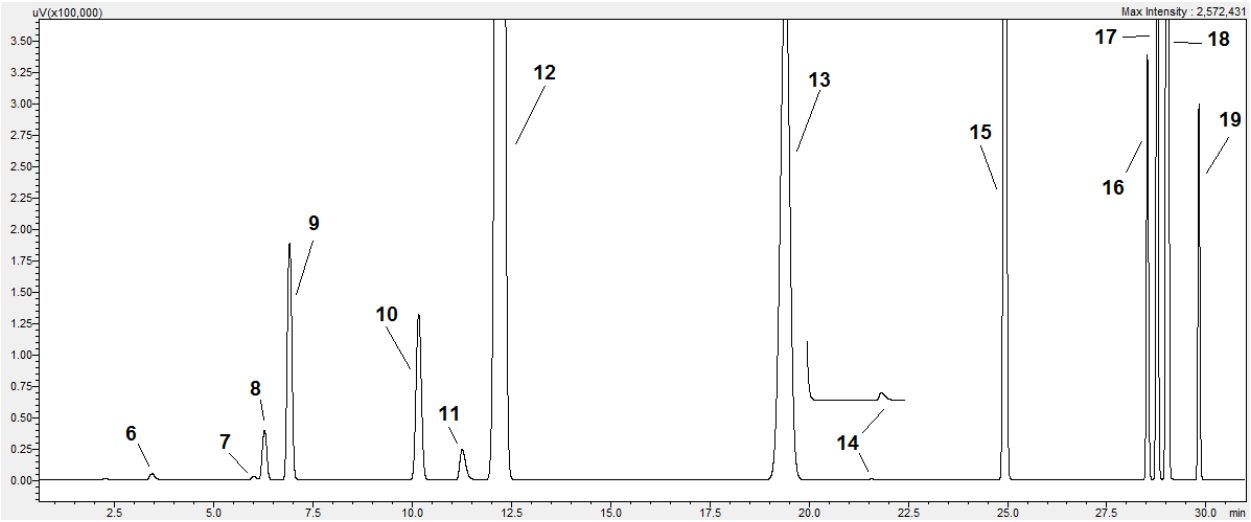

Figure 2: Chromatogram of a Class 2A Standard (data for corresponding peaks can be found in Tables 6 and 7)

Class 2 A	Conc (ppm)	CV (n=6) of Gas Experiment				
Compound		1	2	3	4	5
Methanol[6]	25.00	1.41	2.38	3.04	2.04	1.65
Acetonitrile[7]	3.42	1.56	2.43	3.54	2.11	1.67
Methylene Chloride[8]	5.00	2.77	0.96	2.15	1.54	0.82
trans-1,2-Dichloroethene[9]	7.83	3.21	0.71	2.10	2.01	0.94
cis-1,2-Dichloroethene[10]	7.83	2.97	0.73	2.00	1.79	0.91
Tetrahydrofuran[11]	5.475	1.25	2.44	3.27	1.47	1.26
Cyclohexane[12]	32.33	7.19	2.35	2.67	4.48	1.20
Methylcyclohexane[13]	9.83	9.85	2.82	2.65	5.46	1.25
1,4-Dioxane[14]	3.17	1.48	2.72	3.93	3.60	2.24
Toluene[15]	7.42	1.99	0.60	1.91	2.42	1.03
Chlorobenzene[16]	3.00	1.82	0.62	1.92	2.47	0.99
Ethyl benzene[17]	3.07	4.17	0.57	2.10	3.50	1.13
m-, and p-Xylene[18]	10.85/2.53	4.15	0.55	2.07	3.44	1.14
o-Xylene[19]	1.63	3.66	0.54	2.01	3.33	1.20

Table 6: Coefficient of Variation (CV) for Class 2A Compounds with a G43 USP<467> Gas Chromatography Column

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Class 2 A	Resolution of Gas Experiment				
Compound	1	2	3	4	5
Acetonitrile to Methylene Chloride	1.1	1.1	1.3	1.3	1.2

Table 7: Resolution between Acetonitrile and Methylene Chloride Class 2A Compounds with the G43 USP<467> Gas Chromatography Column.

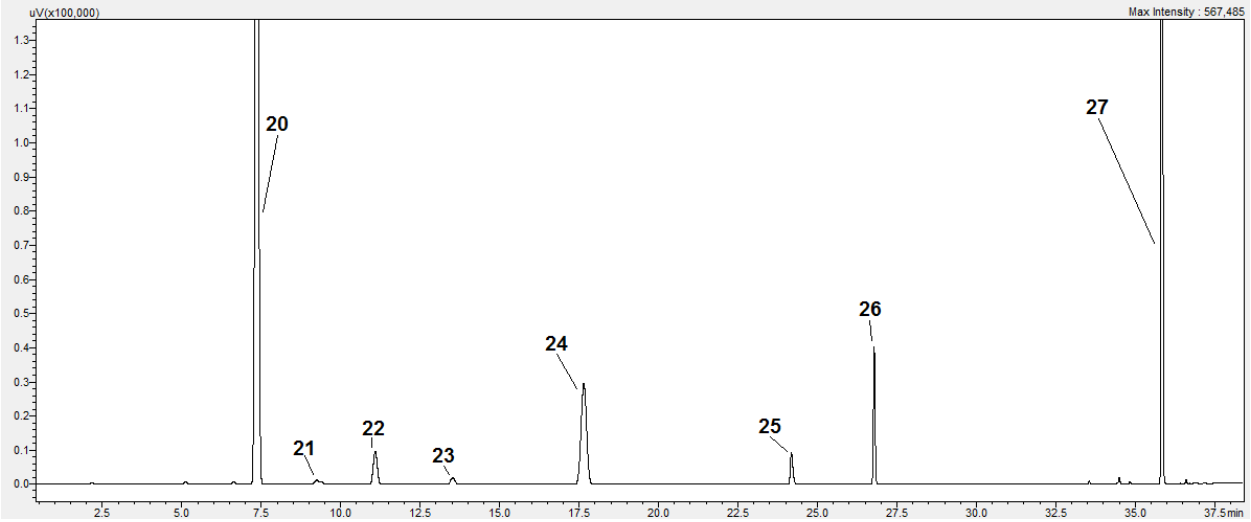

Figure 3: Chromatogram of a Class 2B Standard (data for corresponding peaks can be found in Table 8)

Class 2B	Conc (ppm)	CV (n=6) of Gas Experiment				
Compound		1	2	3	4	5
Hexane[20]	2.42	1.73	2.53	1.83	5.72	2.98
Nitromethane[21]	0.42	1.93	0.99	1.14	3.34	1.58
Chloroform[22]	0.50	0.88	1.91	1.93	3.29	2.29
1,2-Dimethoxyethane[23]	0.83	1.92	5.56	1.57	3.21	1.48
Trichloroethene[24]	0.67	1.18	1.76	2.33	4.18	2.86
Pyridine[25]	1.67	5.53	5.19	10.38	11.38	10.10
2-Hexanone[26]	0.42	1.62	1.99	0.65	1.97	0.63
Tetralin[27]	0.83	1.52	2.45	2.08	3.21	2.71

Table 8: Coefficient of Variation (CV) for Class 2B Compounds with a G43 USP<467> Gas Chromatography Column

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Conclusion

The experiments performed indicate that the Versa delivers a consistent, accurate amount of sample to the GC/FID system for USP<467> Residual Solvents chemical test. Simple changes in the GC parameters influence the CV, S/N and resolution of the residual solvent from USP<467>. Some of the parameters investigated in this study include helium and nitrogen as carrier gas, and linear velocity changes for nitrogen when used as a carrier gas.

All of the CV passed the FDA guidance document requirement of less than 15%. All of the chromatography also passed the USP <467> requirements for S/N ratio and resolution. The resolution between acetonitrile and methylene chloride increased with a change in the nitrogen GC carrier gas linear velocity from 35cm/sec to 25cm/sec.

All other parameters from USP <467>, including sample preparation of the standard in water, were followed for this study.

References

1. A Guide to GC Setup, Restek, http://www.chromspec.com/pdf/lit/rk19.pdf
2. U.S. Department of Health and Human Services, Food and Drug Administration, Guidance for Industry, Bioanalytical Method Validation, May 2001, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

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