USP <467> Headspace Residual Solvent Assay with a HT3™ Headspace Instrument

Application Note

Abstract

The US Pharmacopeia recently released USP<467> as the current monograph for determining residual solvents in pharmaceutical products by static headspace. The USP classified these residual solvents into 3 categories; Class 1, Class 2 and Class 3. This headspace method does not require further validation if the USP parameters are followed.

Following USP<467> monograph parameters, this study utilizes a Teledyne Tekmar HT3 Headspace Instrument (Figure 1) in the static mode, eliminating the need for extensive USP mandated method validation. The Class 1 compounds were evaluated from 50% to 500% of the USP limits. The Class 2 compounds were evaluated from 25% to 400% of the USP limits.

The HT3 met all of the requirements of the recently released USP<467> Residual Solvent headspace monograph for both Class 1 and Class 2 solvents.

Introduction

The monograph classified residual solvents in pharmaceutical products into 3 categories based on their potential health risks. Class 1 solvents are compounds known to have unacceptable toxicities or environmental concerns and should be avoided unless there use can be strongly justified in a risk-benefit assessment. Class 2 solvents are compounds with less severe toxicities and their amounts limited in order to protect patients from potential adverse effects. Class 3 solvents are less toxic and should be used where practical.

The monograph also uses 2 GC columns with different polarities. The USP definition for liquid phase of the G43 column is 6%cyanopropylphenyl – 94%dimethylpolysiloxane. The USP definition for the liquid phase of the G16 polyethyleneglycol (av. Mol. Wt. 15000) is a high molecular weight compound of polyethylene glycol and a diepoxide.

Experimental-Instrument Conditions

The HT3™ headspace instrument was connected to Shimadzu Model GC-2010 GC with FID for this study. A Phenomenex Zebron ZB-624 column, 30m x 0.32mm x 1.8µm was used to meet the G43 column requirement of USP<467>.   A Phenomenex Zebron ZB-WAXplus column, 30m x 0.32mm x 0.25µm was used to meet the G16 column requirement of USP<467>. The Shimadzu flow control was set to the linear velocity option to meet the USP<467> carrier gas flow control requirement of about 35cm/sec for both columns. Employing a 1mm ID inlet split liner provides better performance for use with the headspace analysis.

USP<467> recommends 3 different headspace operating parameters. Headspace operating parameter set 3 was used for this study. The HT3 constant heat headspace method parameter was used to ensure that a new headspace sample was ready after each 60 minute GC run time. Increasing the HT3 oven temperature and the transfer line temperatures by 5°C from the Set 3 parameters improved gas transfer of the compounds as allowed by the USP. Tables 1 display the static HT3 conditions while Table 2 displays the GC/FID parameters for both columns.

HT3 Headspace Instrument Parameters			
Variable	**Value**	**Variable**	**Value**
Constant Heat Time	On	Pressurize	10 psig
GC Cycle Time	70 min	Pressurize Time	0.50 min
Platen/Sample Temp	80°C	Pressurize Equil Time	0.05 min
Valve Oven Temp	110°C	Loop Fill Pressure	5 psig
Transfer Line Temp	110°C	Loop Fill Time	0.20 min
Standby Flow Rate	50mL/min	Inject Time	2.00 min
Sample Equil Time	45.00 min		

Table 1: Static and Dynamic HT3™ Parameters

Shimadzu GC/FID Parameters	
USP G43 Column	Phenomenex® Zebron ZB-624, 30m, 0.32mm ID, 1.8μm; Linear Velocity 35 cm/sec
USP G43 Column Oven Program	35°C for 20 min; 10°C/min to 240°C, hold for 20 min, run time 60 min
USP G16 Column	Phenomenex® Zebron ZB-WAXplus, 30m, 0.32mm ID, 0.25μm; Linear Velocity 35 cm/sec
USP G16 Column Oven Program	50°C for 20 min; 6°C/min to 165°C, hold for 20 min, Run Time 59.17 min
Inlet:	Split Ratio 5:1 for the G43 Column: 15:1 for G16 Column, Temperature 140 °C, Helium Carrier Gas, Linear Velocity 35cm/sec
FID	320°C, Hydrogen Flow 35.0mL/min, Air Flow -400.0mL/min, Constant Column and Makeup Flow – 30mL/min

Table 2: 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 appropriate standard was transferred to 20mL headspace vials containing 5mL of water. Procedure C requires the same concentration as the Procedure A standards to quantitate articles under test. Analyzing the standards in triplicate demonstrates the reproducibility of the method for each compound.

A series of standards were prepared from 50% to 500% of the concentration of the Class 1 Standard prepared as part of the method. Similar standards from 25% to 400% were generated from the Class 2A and 2B standards. Analyzing these samples singularly verified the linearity of the method over these ranges.

Parameters for evaluating the samples are listed in Table 1 and 2.

Results and Conclusions

This study used the Shimadzu GCSolution software Version 2.32 to evaluate the chromatography data. The peak area was used to calculate the %RSD for the triplicate injections of the single standards for each compound. The peak areas were also used to calculate the correlation coefficient r^2 for the linear range of samples for each compound. The signal to noise ratio of all of the Class 1 compounds and the resolution between the acetonitrile and its required peaks were also generated using the Shimadzu GCSolution software.

Table 3 presents the data for the Class 1 compounds with both the G43 and the G16 column required by USP<467>. Figure 2 is the comparison of the USP standard concentration with the G43 and the G16 column. The numbers on the chromatograms correspond to the compound numbers in the tables.

Table 4 presents the data for the Class 2A compounds with both the G43 and the G16 column required by USP<467>. Figure 3 is the comparison of the USP standard concentration with the G43 and the G16 column.

Table 5 presents the data for the Class 2B compounds with both the G43 and the G16 column required by USP<467>. Figure 4 is the comparison of the USP standard concentration with the G43 and the G16 column.

Class 1		G 43 Column			G 16 Column		
Compound	Range (ppm)	S/N	%RSD	r^2	S/N	% RSD	r^2
1,1-Dichloroethene (1)	0.033 to 0.333	54	2.7	0.9990	109	5.0	0.9987
1,1,1-Trichloroethane (2)	0.042 to 0.42	54	0.9	0.9984	78	1.2	0.9984
Carbon Tetrachloride (3)	0.017 to 0.17	4.5	5.6	0.9993		Co elute[A]	
Benzene (4)	0.008 to 0.083	71	2.1	0.9984	98	2.6	0.9994
1,2-Dichloroethane (5)	0.021 to 0.21	52	1.4	0.9998	56	4.1	1.0000

Table 3: Signal to Noise Ratio (S/N), Percent Relative Standard Deviation (%RSD, n=3) and Correlation Coefficient (r^2) Data for the Class 1 Compounds with the G43 and G16 USP<467> Required Gas Chromatography Columns

A – Carbon tetrachloride co elutes with 1,1,1-trichloroethane with the G16 column but is separated from all peaks in the Class 1 standard with the G43 column.
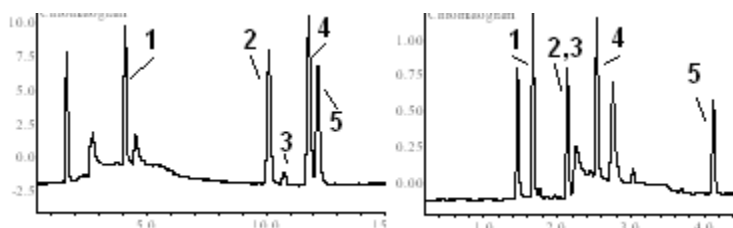
Figure 2: Comparison of the Retention times of the Class 1 Compound at the USP Standard Concentration with the G43 Column (Left) and the G16 Column (Right). The additional peaks are system/DMSO related peaks. The numbers correspond to the compound numbers in Table 3.

Class 2 A			G43 Column			G16 Column	
Compound	Range (ppm)	R	%RSD	r^2	R	% RSD	r^2
Methanol (1)	6.25 to 100		1.3	0.9983		4.1	0.9981
Acetonitrile (2)	0.854 to 10.25	1.0	2.1	0.9983	2.2	2.6	0.9996
Methylene Chloride (3)	1.25 to 20		2.6	0.9997		4.7	0.9976
trans-1,2-Dichloroethene (4)	1.96 to 31.3		2.1	0.9994		5.8	0.9964
cis-1,2-Dichloroethene (5)	1.96 to 31.3		2.2	0.9987		5.3	0.9972
Tetrahydrofuran (6)	1.44 to 17.25		5.1	0.9951		4.2[B]	0.9991
Cyclohexane (7)	8.1 to 97		1.8	0.9978		5.5	0.9960
Methylcyclohexane (8)	2.46 to 29.5		1.2	0.9988		5.2	0.9852
1,4-Dioxane (9)	0.79 to 12.7		0.4	0.9999		9.2	0.9978
Toluene (10)	1.85 to 22.25		1.8	0.9988		5.9	0.9998
Chlorobenzene (11)	0.75 to 9		1.6	0.9990		6.0	0.9986
Ethyl benzene (12)	0.77 to 9.2		0.9	0.9988		6.5	0.9976
p-Xylene (13)	0.63 to 7.6		0.9	0.9990		6.5	0.9978
m-Xylene(14)	2.72 to 32.6		Coelute[C]			6.5	0.9979
o-Xylene (15)	0.41 to 4.9		1.2	0.9989		6.3	0.9992

Table 4: Resolution (R), Percent Relative Standard Deviation (%RSD, n=3) and Correlation Coefficient (r^2) Data for the Class 2A Compounds with the G43 and G16 USP<467> Required Gas Chromatography Columns

B – Tetrahydrofuran is a shoulder on the trans 1,2-dichlororethene peak with the G16 column but is separated from all peaks in the Class 2A standard with the G43 column.

*C – m-Xylene coelutes with p-xylene with the G43 column but is separated from all peaks in the Class 2A stanard with the
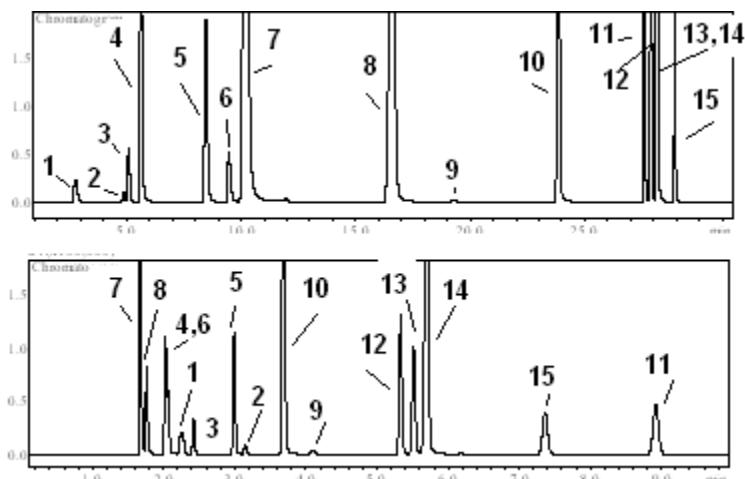G16 column.*

Figure 3: Comparison of the Retention Times of the Class 2A Compounds at the USP Standard Concentration with the G43 Column (Top) and the G16 Column (Bottom). The numbers correspond to the compound numbers in Table 4.

Class 2B		G43 Column		G16 Column	
Compound	Range (ppm)	% RSD	r^2	% RSD	r^2
Hexane (1)	0.121 to 1.45	2.0	0.9940	4.3	0.9820
Nitromethane (2)	0.042 to 0.333	3.6	0.9961	9.1	0.9983
Chloroform (3)	0.025 to 0.4	2.2	0.9995	1.9	0.9994
1,2-Dimethoxyethane (4)	0.083 to 0.667	5.1	0.9958	3.8	0.9997
Trichloroethene (5)	0.033 to 0.533	1.6	0.9989	2.7	0.9984
Pyridine (6)	0.083 to 1.33	9.9	0.9995	3.8	0.9986
2-Hexanone (7)	0.021 to 0.333	2.1	0.9999	5.4	0.9987
Tetralin (8)	0.042 to 0.669	0.8	0.9995	2.2	0.9999

Table 5: Percent Relative Standard Deviation (%RSD, n=3) and Correlation Coefficient (r^2) Data for the Class 2B Compounds with the G43 and G16 USP<467> Required Gas Chromatography Columns
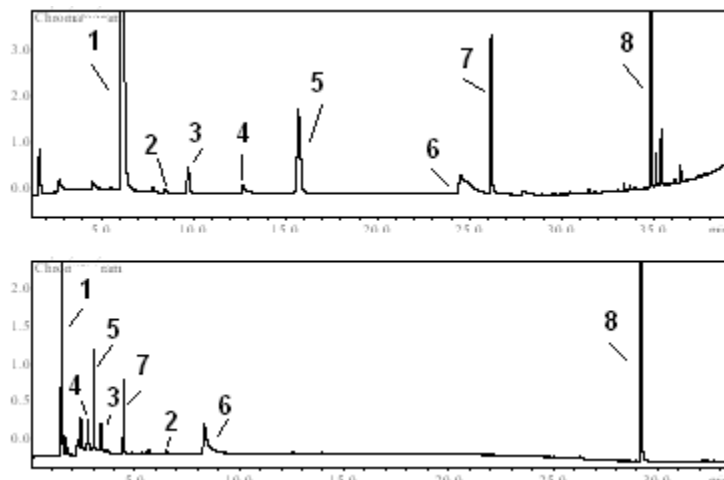
Figure 4: Comparison of the Retention Times of the Class 2B Compounds at the USP Standard Concentration with the G43 Column (Top) and the G16 Column (Bottom). The additional peaks are system/DMSO related peaks. The numbers correspond to the compound numbers in Table 5.

USP Chemical Test Monograph <467> for Residual Solvents was easily validated using the Teledyne Tekmar HT3 headspace instrument with Phenomenex columns and a Shimadzu GC/FID adequately meets the requirements of the recently.

USP 467 Residual Solvent Assey Headspace.docx; 7-Dec-10

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