Headspace Sampling of Residual Solvents per USP 467 Using a Gas Tight Syringe

Application Note

Environmental

Author

Anne Jurek
Applications Chemist
EST Analytical
Cincinnati, OH

Abstract

During the synthesis of some pharmaceuticals it is sometimes necessary to use solvents in order to increase the yield or purity of the product. After the pharmaceutical is produced, the solvent(s) are removed to the greatest extent possible. The products are then tested for any residual solvents in order to limit patient exposure. Residual solvents are separated into classes according to the risk to patient health. Class 1 solvents are to be avoided at all costs as they are known to be human carcinogens or have adverse effects on the environment. Class 2 solvents have less severe toxicities but should be avoided because of the potential of adverse effects. Finally, Class 3 solvents have low toxicity and can be used when needed as long as they are below established limits. Pharmaceutical manufacturers are required to test for residual solvents in order to ensure that any residual solvents in the product are below established exposure limits. United States Pharmacopeia (USP) general chapter <467> describes a static headspace gas chromatography procedure for the determination of residual solvents. This application will demonstrate the USP <467> procedure using an autosampler configured with a gas tight syringe for static headspace sampling.

Introduction:

It is recommended that, whenever possible, Class 1 residual solvents not be used. However, sometimes this is unescapable. In this case, the solvent needs to be identified and quantified. Class 2 residual solvents, on the other hand, have to be present above the prescribed limits before testing is required. Typically drug companies calculate the collective level of residual solvents that are contained within the reactants of the drug manufacturing process. If the calculation shows the residual solvents to be below the prescribed levels, no further testing is needed. However, if the calculation results in levels above the acceptable limits; further testing is required.

In order to test for residual solvents, it is common to couple a Gas Chromatograph/Flame Ionization Detector (GC/FID) to a headspace sampling system. Two columns are required for this analysis; one for initial testing and one for confirmation. This investigation will use the FLEX gas tight syringe based headspace sampling system together with an Agilent 7890A GC/FID.

Experimental:

The FLEX Autosampler was affixed onto an Agilent 7890A GC/FID. A 2.5ml syringe was installed in the FLEX for headspace sampling. Two different columns were ordered from Restek. The Rxi®-624 Sil MS 30m x 0.32mmID x 1.8μm column was used for analyte detection, while the Stabilwax®-DA 30m x 0.25mmID x 0.25μm column was

employed as the confirmation column. Refer to Tables 1 and 2 for the FLEX Autosampler conditions and the GC/FID parameters respectively.

FLEX	Parameters
General	
Method Type	Headspace
Sample Incubate Agitate	
Incubation Temp.	80ºC
Incubation Time	60min
Agitation Type	Orbital
Agitation Speed	100%
Agitation Duration	59.9min
Agitation Delay	0.1min
Sample Fill	
Syringe Temperature	90ºC
Syringe Needle Depth	90%
Sample Depth Speed	20%
Sample Volume	1000µl
Sample Fill Rate	2%
Sample Fill Delay	2sec
Wait	
Wait on Input	GC Ready
Injection	
Needle Depth Speed	80%
Needle Depth	100%
Injection Rate	10%
Injection Volume	1000µl
Pre-Injection Delay	1sec
Post-Injection Delay	1sec
Injection Start Output	Start
Sweep Needle	
Needle Temperature	Ambient
Needle Sweep Time	0.1min
Syringe Pumps	2
Syringe Pump Volume	1875µl
Syringe Pump Speed	50%

Table 1: FLEX Autosampler Experimental Parameters

GC/FID	Agilent 5890
Inlet Temperature	140°C
Inlet Pressure	10.183psi
Gas	Helium
Inlet	Split/Splitless
Split Ratio	5:1
Column Flow	2.2ml/min
Column 1	Rxi®-624 Sil MS 30m x 0.32mmID x 1.8µm
Column 2	Stabilwax®-DA 30m x 0.25mmID x 0.25µm
Inlet Liner	1mm ID x 78.5mm L x 6.3mm OD Straight Sky Liner
Oven Program	40°C hold for 20 min, ramp 10°C/min to 240°C hold for 20 min, 60 min total runtime
FID Temperature	250°C

Table 2: GC/FID Experimental Parameters

All of the USP <467> standards were ordered from Restek and prepared as follows:

Class 1 Standard Stock Solution

Add 9mls of dimethyl sulfoxide to a 100ml volumetric flask. Transfer 1ml of Class 1 standard into the 100ml volumetric flask and fill the flask to volume with reagent water. Next, take 1ml of this mix and add it to a 100ml volumetric flask previously filled with 50mls of reagent water. Fill this flask to volume. Finally, transfer 10mls of the second volumetric to a third 100ml volumetric flask filled with 50mls of reagent water and bring to volume.

Class 1 Standard Solution

Transfer 1ml of Class 1 Standard Stock Solution to a 20ml headspace vial containing 5mls of reagent water. Cap, seal, mix and place the sample into the FLEX autosampler 20ml tray.

Class 2 Mix A Standard Stock Solution

Transfer 1ml of Class 2 Mix A standard into a 100ml volumetric flask previously filled with 50mls of reagent water and dilute to volume.

Class 2 Mix A Standard Solution

Transfer 1ml of Class 2 Mix A Standard Stock Solution to a 20ml headspace vial containing 5mls of reagent water. Cap, seal, mix and place the sample into the FLEX autosampler 20ml tray.

Class 2 Mix B Standard Stock Solution

Transfer 1ml of Class 2 Mix B standard into a 100ml volumetric flask previously filled with 50mls of reagent water and dilute to volume.

Class 2 Mix B Standard Solution

Transfer 5mls of Class 2 Mix B Standard Stock Solution to a 20ml headspace vial containing 1ml of reagent water. Cap, seal, mix and place the sample into the FLEX autosampler 20ml tray.

Each standard solution was run three times on each column and analyzed to determine the precision of the sampling and analysis and to ensure the results met the required signal to noise and resolution requirements of the USP<467> method. Figures 1 through 6 displays labeled chromatograms of the residual solvent classes and mixes while Tables 3 through 8 shows the precision of the experimental results.

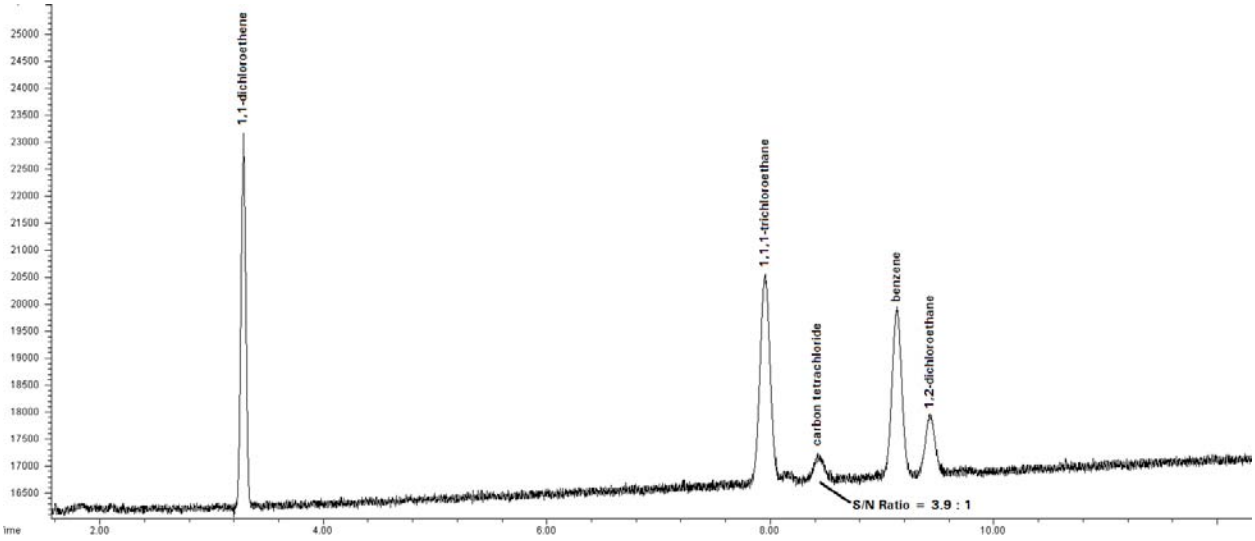

Figure 1: Class 1 Residual Solvent Chromatogram on an Rxi-624 Column

Class 1 Residual Solvents Rxi-624 Column	
Compound	**%RSD**
1,1-Dichloroethene	4.30
1,1,1-Trichlorethane	4.23
Carbon Tetrachloride	3.15
Benzene	3.66
1,2-Dichloroethane	5.81

Table 3: Class 1 Residual Solvent Precision Table on an Rxi-624 Column

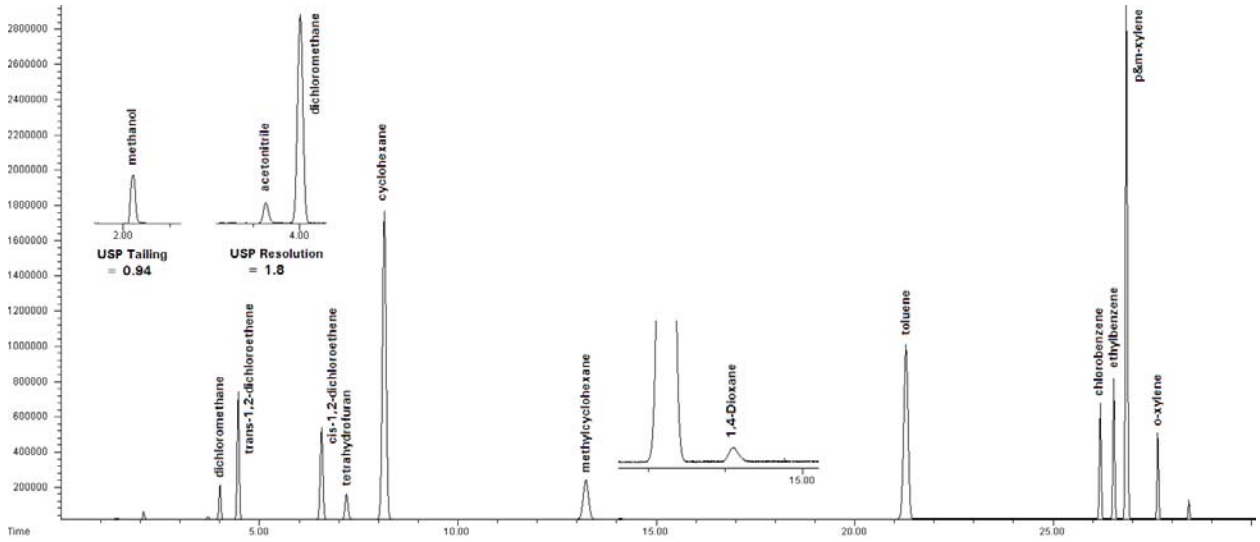

Figure 2: Class 2 Mix A Residual Solvent Chromatogram on an Rxi-624 Column

Class 2 Mix A Residual Solvents Rxi-624 Column	
Compound	**%RSD**
Methanol	1.84
Acetonitrile	2.50
Dichloromethane	0.83
trans-1,2-Dichloroethene	0.32
cis-1,2-Dichloroethene	0.60
THF	1.09
Cyclohexane	3.29
Methylcyclohexane	2.72
1,4-Dioxane	1.67
Toluene	0.54
Chlorobenzene	0.44
Ethylbenzene	0.82
p&m-Xylene	0.77
o-Xylene	0.62

Table 4: Class 2 Mix A Residual Solvent Precision Table on an Rxi-624 Column

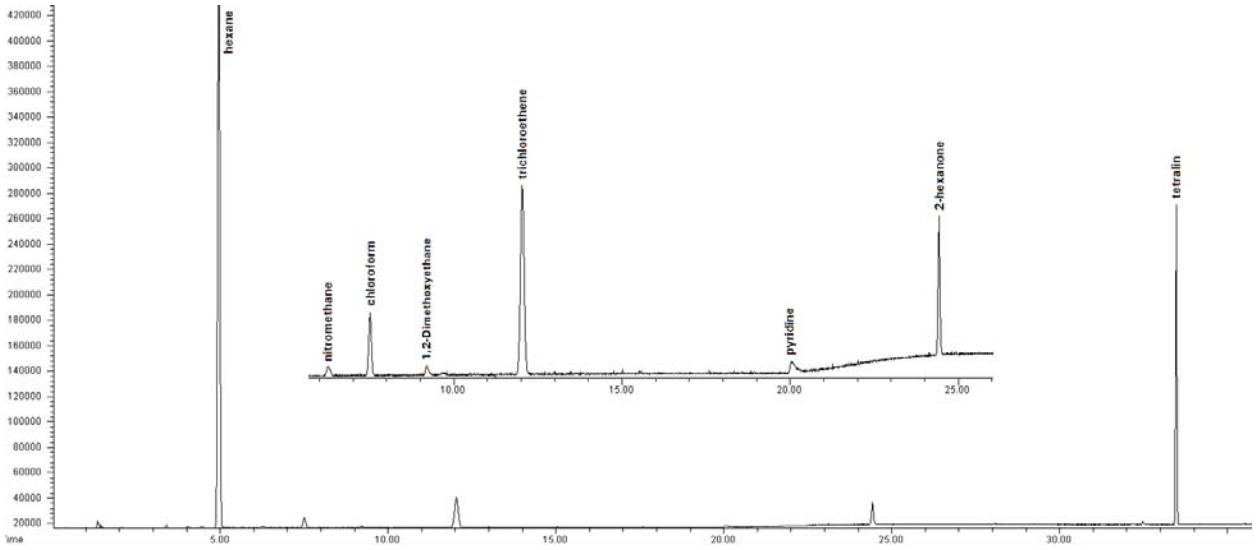

Figure 3: Class 2 Mix B Residual Solvent Chromatogram on an Rxi-624 Column

Class 2 Mix B Residual Solvents Rxi-624 Column	
Compound	**%RSD**
Hexane	0.81
Nitromethane	2.75
Chloroform	1.40
1,2-Dimethoxyethane	0.66
Trichloroethene	1.27
Pyridine	3.28
2-Hexanone	1.40
Tetralin	0.61

Table 5: Class 2 Mix B Residual Solvent Precision Table on an Rxi-624 Column

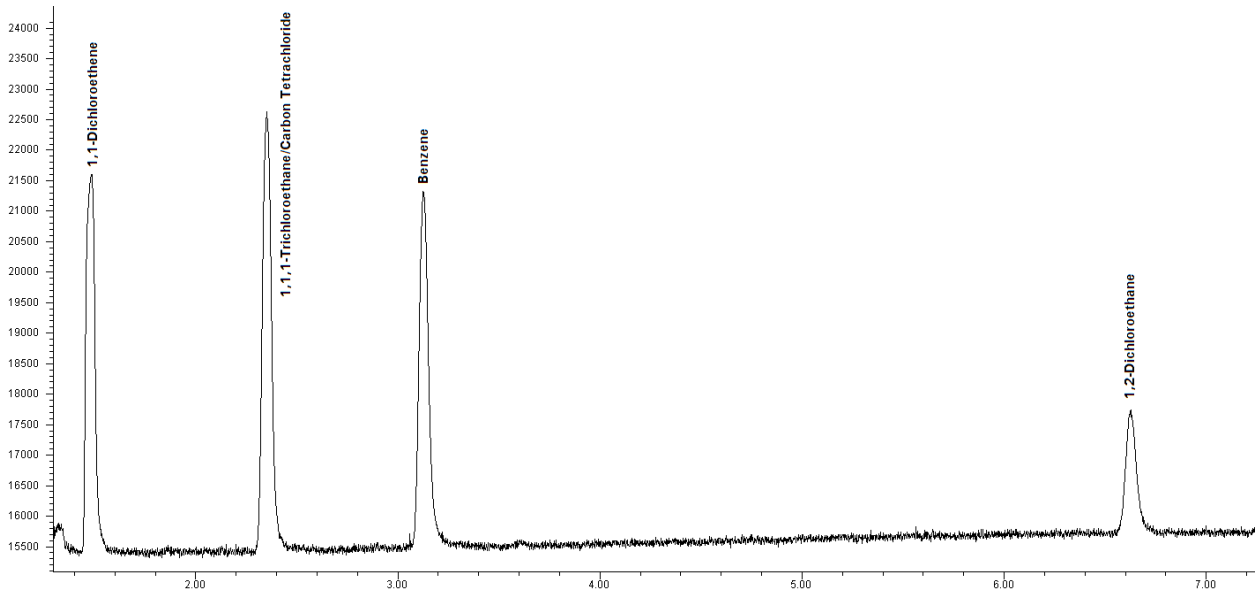

Figure 4: Class 1 Residual Solvent Chromatogram on a Stabilwax Column

Class 1 Residual Solvents Stabilwax Column	
Compound	**%RSD**
1,1-Dichloroethene	2.95
1,1,1-Trichlorethane/Carbon Tetrachloride	1.57
Benzene	2.57
1,2-Dichloroethane	1.24

Table 6: Class 1 Residual Solvent Precision Table on a Stabilwax Column

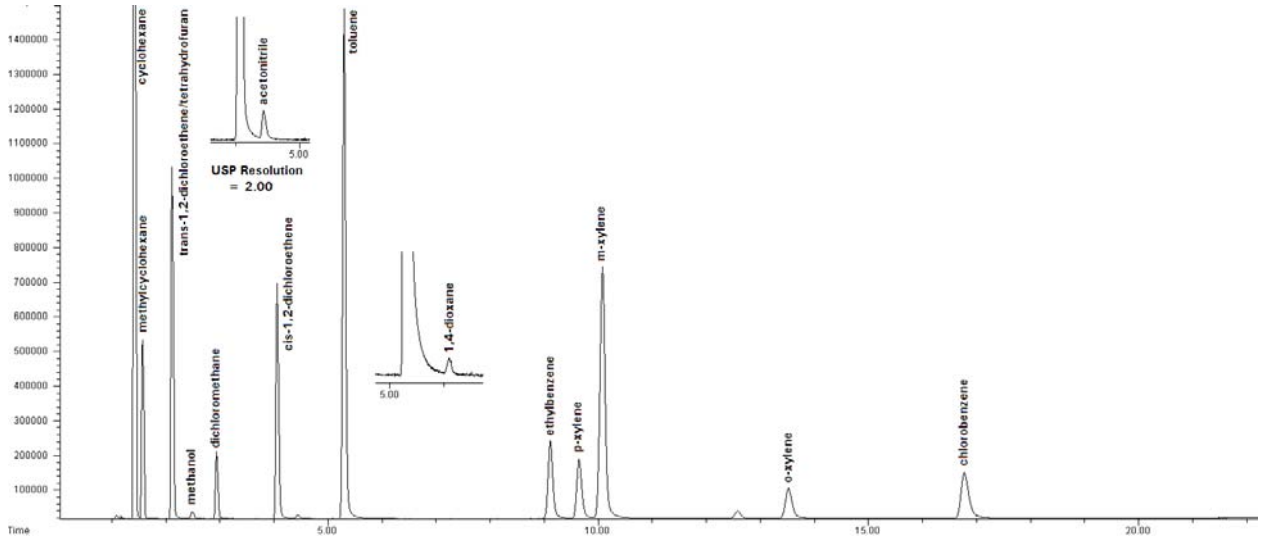

Figure 5: Class 2 Mix A Residual Solvent Chromatogram on a Stabilwax Column

Class 2 Mix A Residual Solvents Stabilwax Column	
Compound	**%RSD**
Methanol	1.81
Acetonitrile	1.63
Dichloromethane	2.19
trans-1,2-Dichloroethene/tetrahydrofuran	1.97
cis-1,2-Dichloroethene	2.16
Cyclohexane	1.51
Methylcyclohexane	1.46
1,4-Dioxane	1.26
Toluene	1.96
Chlorobenzene	2.09
Ethylbenzene	1.79
p-Xylene	1.85
m-Xylene	1.75
o-Xylene	2.20

Table 7: Class 2 Mix A Residual Solvent Precision Table on a Stabilwax Column

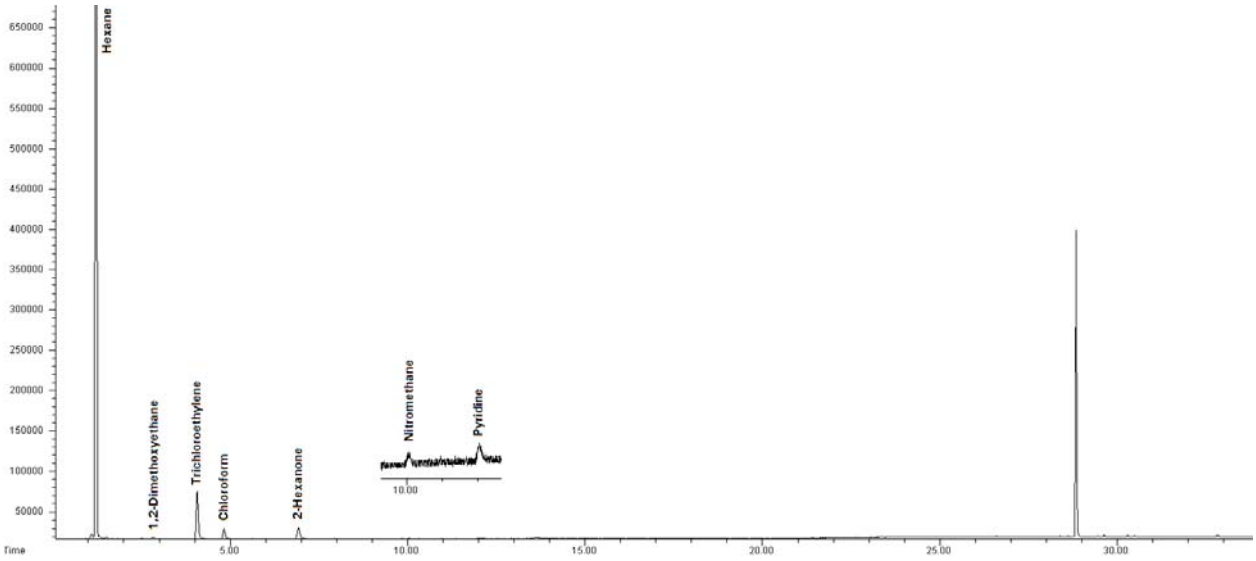

Figure 5: Class 2 Mix B Residual Solvent Chromatogram on a Stabilwax Column

Class 2 Mix B Residual Solvents Stabilwax Column	
Compound	%RSD
Hexane	1.73
Nitromethane	3.15
Chloroform	0.36
1,2-Dimethoxyethane	1.49
Trichloroethene	0.66
Pyridine	0.48
2-Hexanone	1.20
Tetralin	1.87

Table 7: Class 2 Mix B Residual Solvent Precision Table on a Stabilwax Column

Conclusions:

In order to test for residual solvents it is essential to have a reliable and accurate sampling and analysis system. This study proved the FLEX syringe based headspace sampling system to be an exceptional platform for performing USP<467> sample introduction. The results displayed excellent reproducibility and met all of the method requirements for signal to noise and compound resolution thus making the FLEX an asset to any laboratory performing this analysis.

References:

Chemical Tests / (467) Residual Solvents, July 1, 2007, Web June 1, 2015, http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/generalChapter467Current.pdf

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