



Introduction

Residual solvents have had official limits in the United States as set in USP 30 <467>. The traditional method for the residual solvents test is the Headspace-Gas Chromatography/Flame Ionization Detector (Headspace-GC/FID). Continuing challenges of the Headspace-GC/FID method include separation of co-eluting compounds, identification of unknown or unexpected contaminants, and quantification of solvents at trace level. It was the objective of this study to determine a procedure utilizing a Headspace-Gas Chromatography/Mass Spectrometer (Headspace-GC/MS) that could effectively identify and quantitate class 1, 2 and, 3 residual solvents to streamline the screening process for new bulk and finished products. Seven residual solvents (methanol, ethanol, acetone, acetonitrile, methylene chloride, benzene, and heptane) were chosen as representative of Class 1, 2 and 3 residual solvents. A case study screening Acetaminophen for residual solvents demonstrated the advantages of the Headspace-GC/MS methodology.

Development

GC column of DB-624 was selected as a general-purpose column for volatiles featuring a low bleed. This column improves signal to noise ratio, thus leading to better sensitivity. Electron Ionization (EI) was chosen as the desired mode due to reproducibility of spectra in addition to the large cross-referencing capability against the standard NIST library. DMSO was chosen as the sample solvent due to its ability to dissolve a wide range of compounds. The seven chosen solvents were prepared at five concentration levels, and injected on the GC/MS system. From these injections, linearity, limit of detection, limit of quantitation, and % Bias information was determined and presented in **Table 1**. A typical chromatogram is presented in **Figure 1**. A plot of the linearity information is presented in **Figure 2**. The information indicates that the method is sensitive and linear.

Methodology

GC/MS System: Agilent, 6890N GC with MS 5973 Inert XL Mass Selective Detector. EI Mode.

Data Analysis: Software: G1701DA ChemStation, Revision Code: D.02.00.

Column: J & W Scientific, DB-624, 20 m x 0.18 mm ID, 1.00 mm film thickness.

Oven Temp Program: 35°C hold 5 min, 35°C to 160°C at 20°C/min, 160°C to 240°C at 35°C/min hold 7 min.

Total Run Time: 20.5 min.

Injection Temp: 140°C.

MS Detector Temp: 230°C.

Flow Rate: 0.7 mL/min.

Split Ratio: 100:1

Autosampler: Agilent, G1888 Network Headspace Sampler.

Headspace Conditions: Oven Temp: 120°C, Loop Temp: 130°C, Transfer Line Temp: 135°C.

Results

Table 1: System Suitability, Linearity, Bias, LOD and LOQ

No.	Solvent Name	USP Class	Retention Time (min)	System Suitability (RSD, %)	Linearity (r ²)	Bias (%)	LOD (ppm)	LOQ (ppm)
1	Methanol	2	1.72	2.0	1.000	1.8	0.27	0.80
2	Ethanol	3	2.39	2.2	1.000	0.65	0.30	0.90
3	Acetone	3	2.80	2.7	1.000	2.1	0.34	1.0
4	Acetonitrile	2	3.15	3.1	1.000	8.1	0.40	1.2
5	Methylene Chloride	2	3.36	2.8	0.999	0.94	0.50	1.5
6	Benzene	1	6.74	4.0	0.998	0.51	1.0	3.0
7	Heptane	3	7.12	2.6	1.000	0.31	0.40	1.2

Figure 1: Example Standard Chromatogram with Seven Residual Solvents

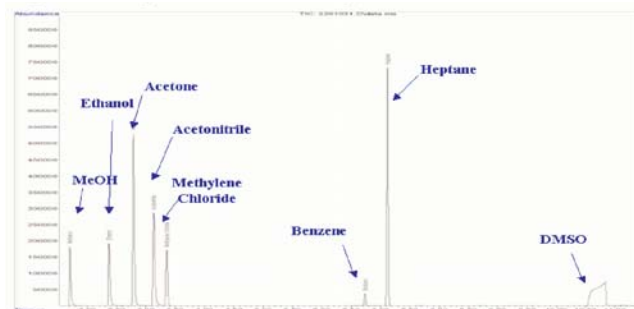


Figure 3: Acetaminophen in DMSO Chromatogram

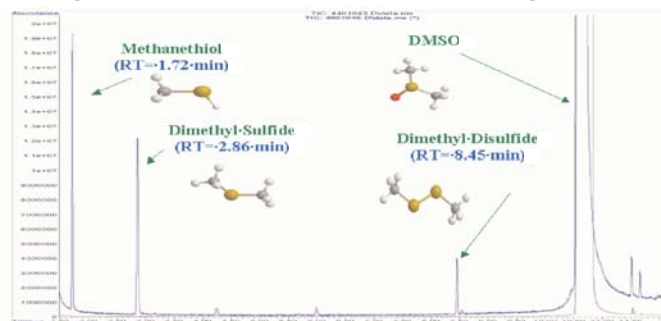


Figure 7: Acetaminophen Spiked with 5ppm of 7 Residual Solvents

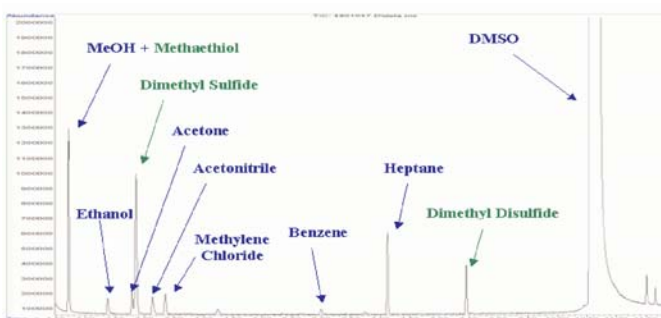


Figure 2: Linearity Plots of Seven Residual Solvents

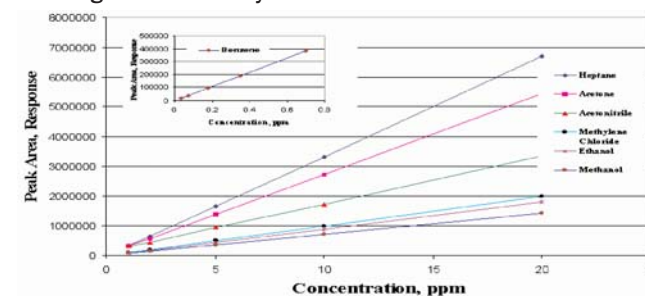


Figure 4: Acetaminophen in DMSO, Identification of Peak @ RT=1.72 min

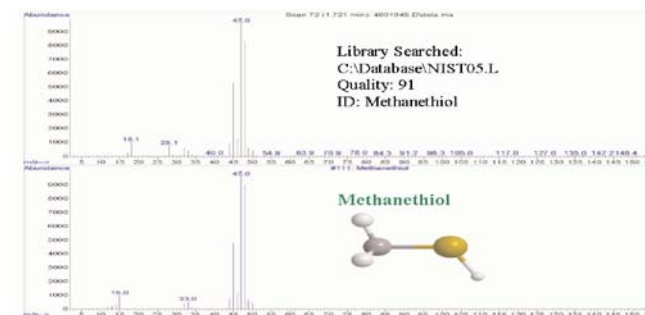


Figure 5: Acetaminophen in DMSO, Identification of Peak @ RT=2.86 min

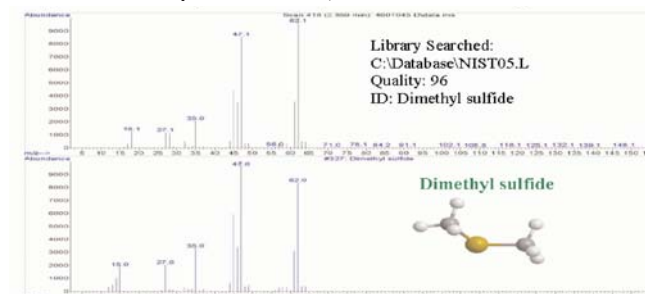
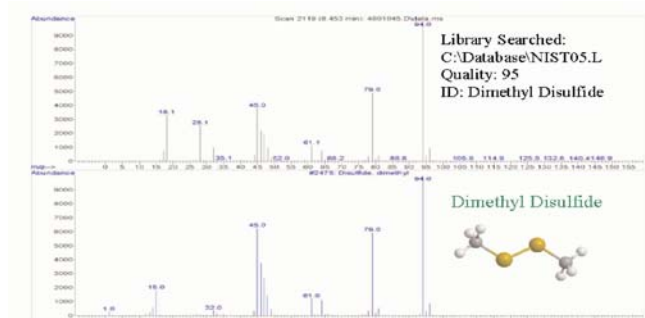


Figure 6: Acetaminophen in DMSO, Identification of Peak @ RT=8.45 min



Screening Study

After the method was developed and demonstrated to be sensitive and linear, an active pharmaceutical ingredient was dissolved and injected on the chromatographic system. For this example, acetaminophen was chosen to simulate receipt of a raw material for residual solvents screening. A DMSO blank was also prepared to determine peaks attributed solely to the API. The overlaid chromatogram is presented in **Figure 3**. The ion trace mass spectra data was then compared to the NIST library for identification, as illustrated in **Figure 4**, **Figure 5**, and **Figure 6**. Three residual solvents were identified. The seven representative residual solvents were then spiked into an API sample preparation and is presented in **Figure 7**. As can be seen, methanol co-eluted with the methanethiol present in the API, and acetone eluted close enough to dimethyl sulfide to potentially cause a misidentification if relying on retention time data alone.

Conclusion

1. This study indicated that the Headspace-GC/MS methodology is sensitive, selective, and accurate based on system suitability, linearity, LOD and LOQ results.
2. The Headspace-GC/MS technique provides a means to identify unknown or unexpected residual solvents, and avoids the possibility of misidentifying residual solvents solely on retention time.
3. The Headspace-GC/MS technique provides a more streamline and efficient approach to screening residual solvents, offering the ability to identify and quantitate residual solvents in a single step as opposed to the current USP method which is divided into three procedures.

References

1. USPC Method 30-NF 25 Through First Supplement: General Chapters: <467>- Organic Volatile Impurities, 8/1/2007
2. Aryo Nikopour, "Residual Solvents: Screening Methodologies", USP 2007 Annual Meeting; Tampa, Florida, 09/27/2007.