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Application Note SI-01584

Determination of Residual Solvents Using USP <467>

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Introduction

In the United States pharmaceutical market, all drug substances, excipients and products are subject to control of residual solvents under US Pharmacopeia method <467>, revised with effect July 1, 2008. The test method involves an analytical cascade covering 53 solvents grouped in three classes of descending toxicity; Class 1 (solvents that should not be used), Class 2 (solvents of limited use) and Class 3 (solvents not known to present a health hazard <5000 ppm). The method involves screening the product for all of the solvents in Class 1 and Class 2 (procedure A). If compounds are detected and exceed their concentration limit the sample is reanalyzed using a different polarity GC column (procedure B). If the presence of a solvent is confirmed by procedure B then the sample is analyzed once more to quantify the amount (procedure C).

This note demonstrates the excellent performance of the Varian 450-GC Gas Chromatograph/CombiPAL headspace system and the chromatographic performance of the Varian VF-624ms and VF-WAXms columns in the analysis of some Class 1 and Class 2 solvents under USP <467>.

Method

The minimum requirements in USP <467> for procedure A and B are defined as:

Procedure A

1. Signal-to-noise (S/N) ratio for Class 1 chemicals > 3
2. Signal-to-noise ratio, 1,1,1-trichloroethane (Class 1) > 5
3. Resolution of acetonitrile/dichloromethane (Class 2 mix A) > 1.0

Procedure B

1. Signal-to-noise ratio for benzene (Class 1) > 5
2. Resolution of acetonitrile/*cis*-dichloroethene (Class 2 mix A) > 1.0

S/N ratios are qualifiers for determining system sensitivity while the resolution parameter is a quality check on chromatographic performance for important separations.

Instrumentation

GC: Varian 450-GC Gas Chromatograph
Headspace Sampler: CombiPAL
Columns:
Procedure A: VF-624ms, fused silica, 30 m x 0.32 m, df = 1.80 µm (CP9104)
Procedure B: VF-WAXms, fused silica, 30 m x 0.32 mm, df = 0.25 µm (CP9212)
Injection: Split
Detection: FID, 250 °C
Software: Galaxie™ Software for GC control and data handling

Conditions Procedure A

Sample: USP <467> Standard Solutions, in 20 mL headspace vial
Carrier Gas: Helium, constant flow
Flow Rate: 2.0 mL/min
Temperature: 40 °C for 20 min, to 240 °C at 10 °C/min, maintain for 20 min
Injector: Split 1:5, 140 °C

Conditions Procedure B

Sample: USP <467> Standard Solutions, in 20 mL headspace vial
Carrier Gas: Helium, constant flow
Flow Rate: 2.0 mL/min
Temperature: 50 °C for 20 min, to 165 °C at 6 °C/min, maintain for 20 min
Injector: Split 1:5, 140 °C

Headspace Conditions, Procedure A & B

Equilibration Temp: 80 °C
Equilibration Time: 45 min
Injection Volume: 1 mL
Syringe Temp: 100 °C

Samples

Aqueous standard solutions were prepared according to method guidelines from third party purchased USP <467> test mixtures.

Results and Discussion

The headspace/GC system passes the minimum S/N specifications in the USP<467> suitability test for all Class 1 chemicals. The FID response for carbon tetrachloride is, as can be expected, relatively poor. This is reflected in the low S/N ratio (Figure 1). The S/N ratio specification for benzene for procedure B (Figure 4) is easily met by the CombiPAL/Varian 450-GC combination. In addition, the resolution between acetonitrile/dichloromethane on the VF-624ms column of 1.9 easily passes the USP <467> criterion for this parameter which is set at 1.0 (Figure 2a).

The basic properties of pyridine (Class 2 mixture B) make it the most challenging analyte in the USP <467> method in terms of column inertness. Although not perfectly symmetrical, the peak shape of pyridine obtained on the VF-624ms is excellent for this type of "624" column (Figure 3a). The quality peak shape will facilitate improved detection and quantification for low pyridine impurity levels.

The resolution requirement for the acetonitrile/*cis*-1,2-dichloroethene separation in procedure B (Rs > 1.0) is easily exceeded by the VF-WAXms column (Rs > 3.0) which exhibits good selectivity and efficiency for this key separation (Figure 5).

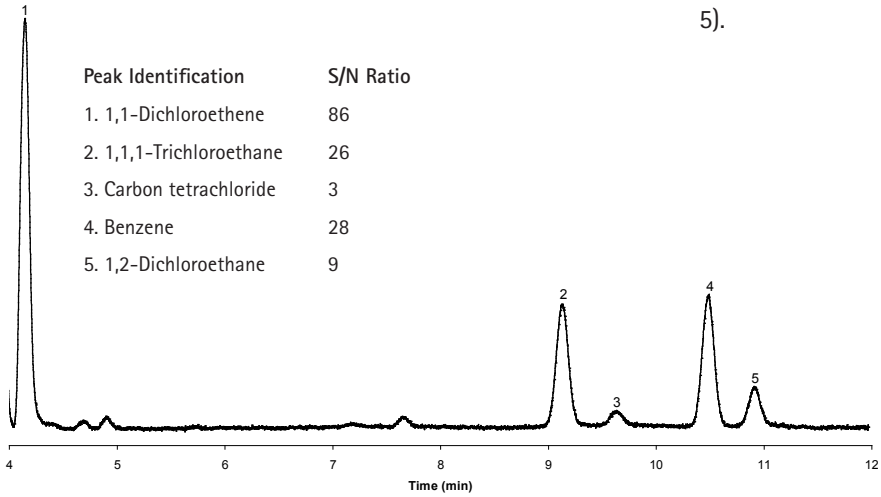


Figure 1. Procedure A. Class 1 Standard Solution.

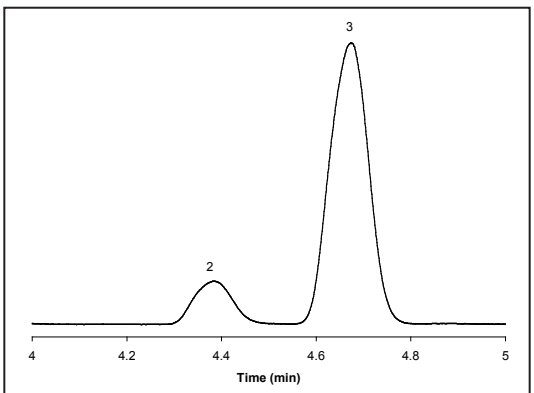


Figure 2a. Procedure A. Class 2 Mixture A Standard Solution, Resolution acetonitrile/dichloromethane.

Figure 2. Procedure A. Class 2 Mixture A Standard Solution.

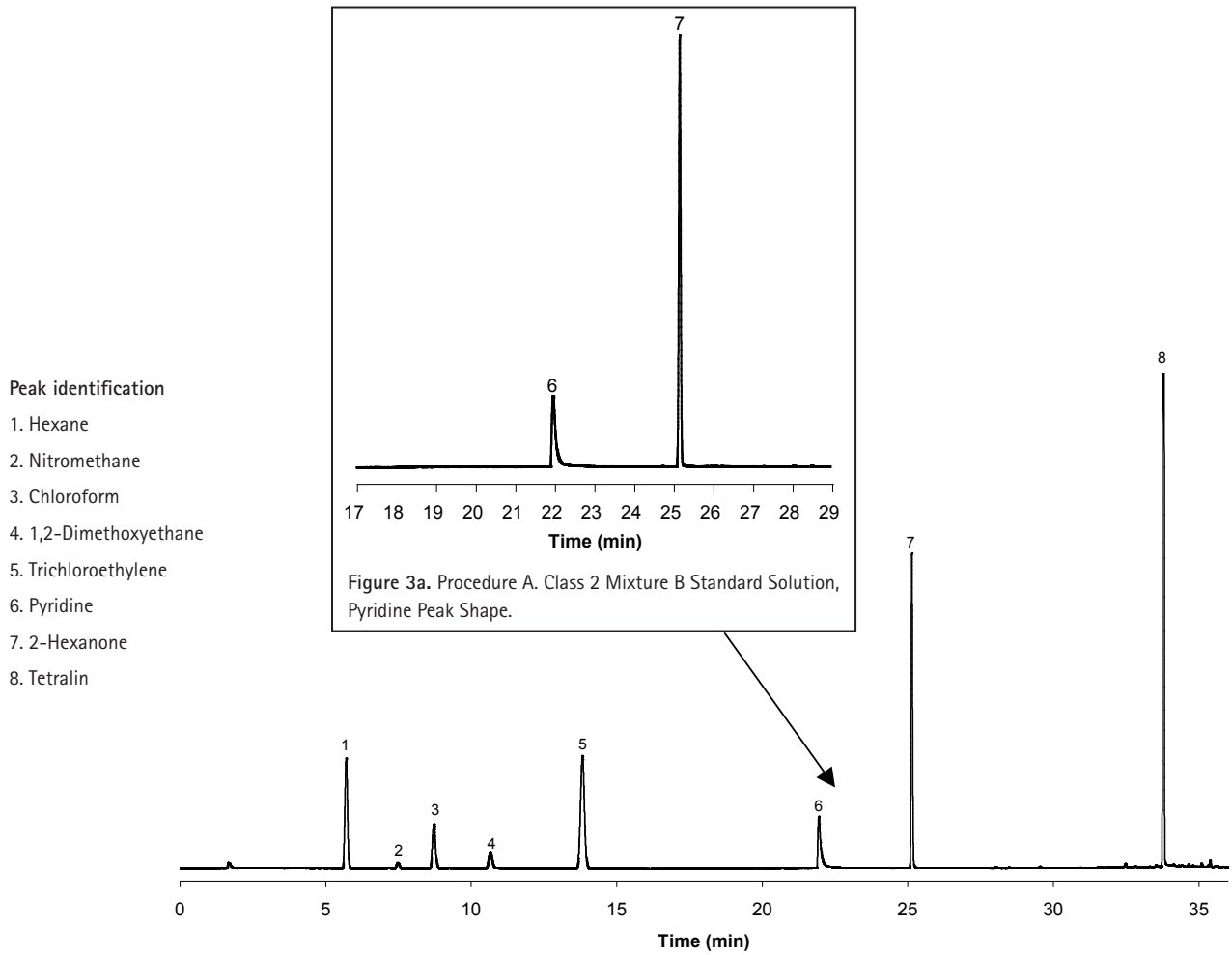
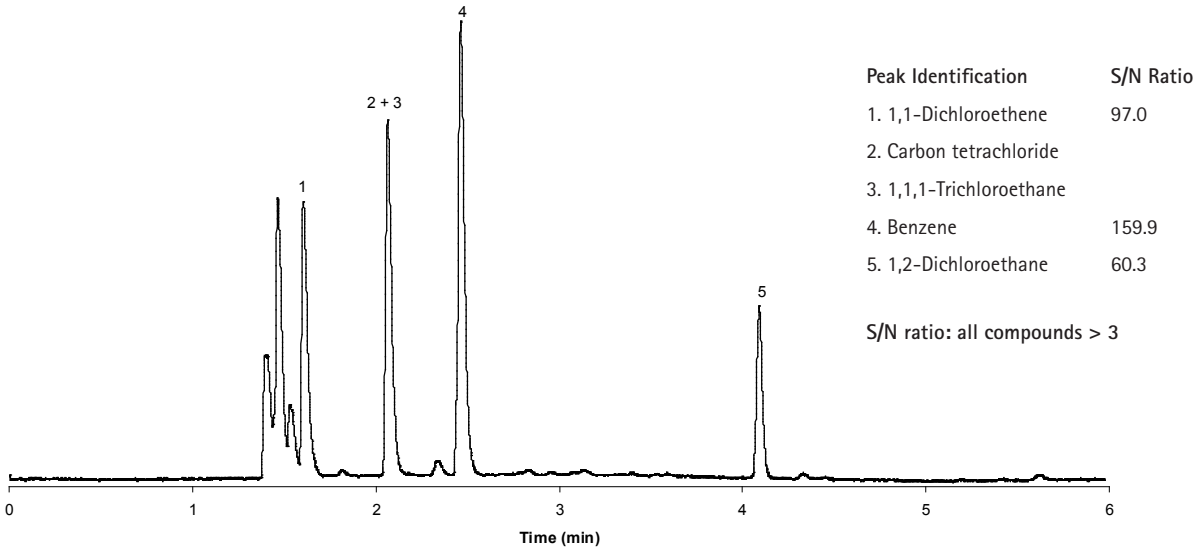


Figure 3a. Procedure A. Class 2 Mixture B Standard Solution, Pyridine Peak Shape.

Figure 3. Procedure A. Class 2 Mixture B Standard Solution.



Peak Identification	S/N Ratio
1. 1,1-Dichloroethene	97.0
2. Carbon tetrachloride	
3. 1,1,1-Trichloroethane	
4. Benzene	159.9
5. 1,2-Dichloroethane	60.3

S/N ratio: all compounds > 3

Figure 4. Procedure B. Class 1 Standard Solution.

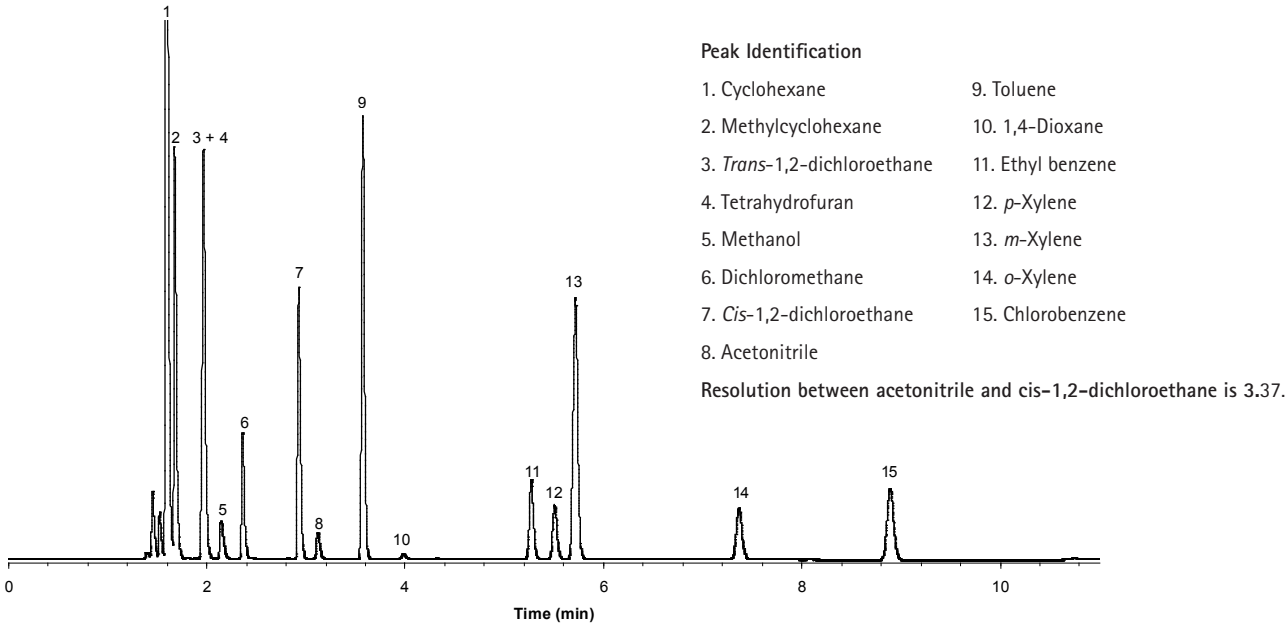


Figure 5. Procedure B. Class 2 Mixture A Standard Solution.

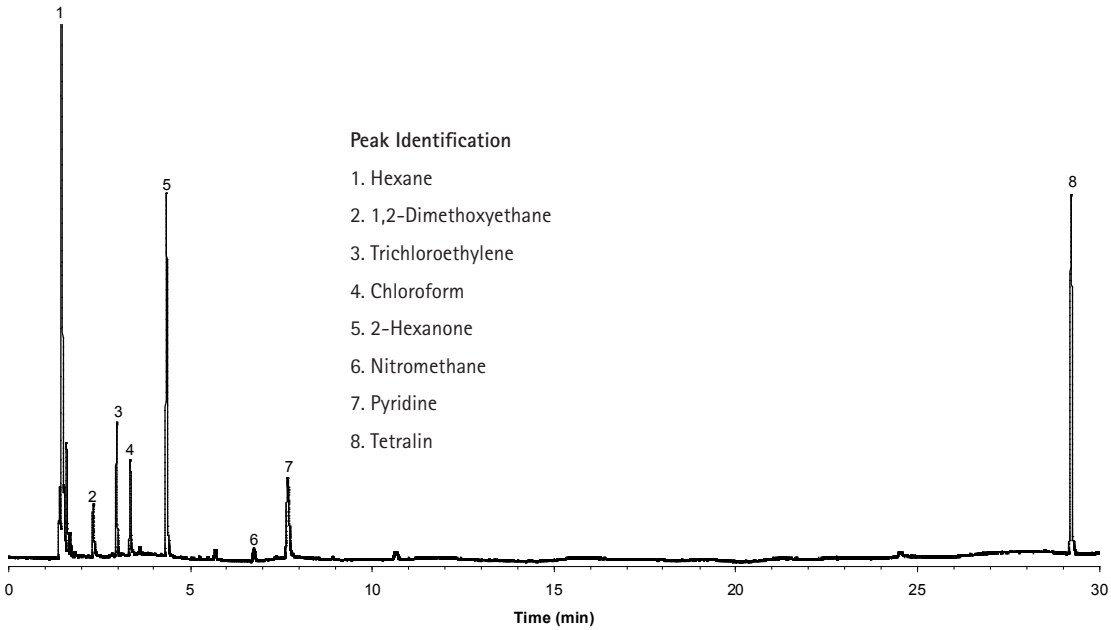


Figure 6. Procedure B. Class 2 Mixture B Standard Solution.

Conclusion

The sensitivity and good response of Varian 450-GC/Combipal headspace unit combined with the VF-WAXms and VF-624ms columns for high performance in resolution and inertness managed by the Galaxie™ software provide an excellent platform for the the analysis of residual solvents required by USP <467>.

References

USP <467> (2008) Residual Volatile Impurities. United States Pharmacopeia, Maryland, USA.

These data represent typical results.
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