Application Note

Residual Solvent

Analysis of USP Method <467> Residual Solvents on the Agilent 8890 GC System

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Abstract

This Application Note highlights the use of the Agilent 8890 GC and the Agilent J&W DB-Select 624 UI for 467 and Agilent J&W HP-INNOWax columns in the detection and confirmation of <467> residual solvents. The system meets all specifications required in USP Method <467>, and demonstrates excellent repeatability across several injections.

Introduction

Class 1 and class 2 residual solvents must be monitored and regulated, and the method for the analysis of these solvents involves three procedures:

- **Procedure A:** Initial identification and limit test using a G43 phase column (in this case, Agilent J&W DB-Select 624 UI for 467)
- **Procedure B:** If above limit in procedure A, perform a confirmation of peak identity and secondary limit test using a G16 phase column (in this case, Agilent J&W HP-INNOWax)
- **Procedure C:** If above limit in procedures A and B, perform a quantification using whichever column provided fewer coelutions

This Application Note analyzed residual solvents listed in USP Method <467> with the Agilent 8890 GC. The J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns were used in this analysis, and configured with dual flame ionization detectors (FIDs). Therefore, procedures A and B could be run simultaneously with one injection.

Experimental

Equipment

An 8890 GC was configured with a split/splitless inlet (SSL) and dual FIDs, and sampling was performed using an Agilent 7697A headspace sampler. An inert tee was used to split the flow equally between the two columns, with both columns leading directly to FIDs. Figure 1 shows the complete configuration.

Chemicals and reagents

Dimethyl sulfoxide (99.9 %) and water (HPLC grade) were purchased from Sigma-Aldrich.

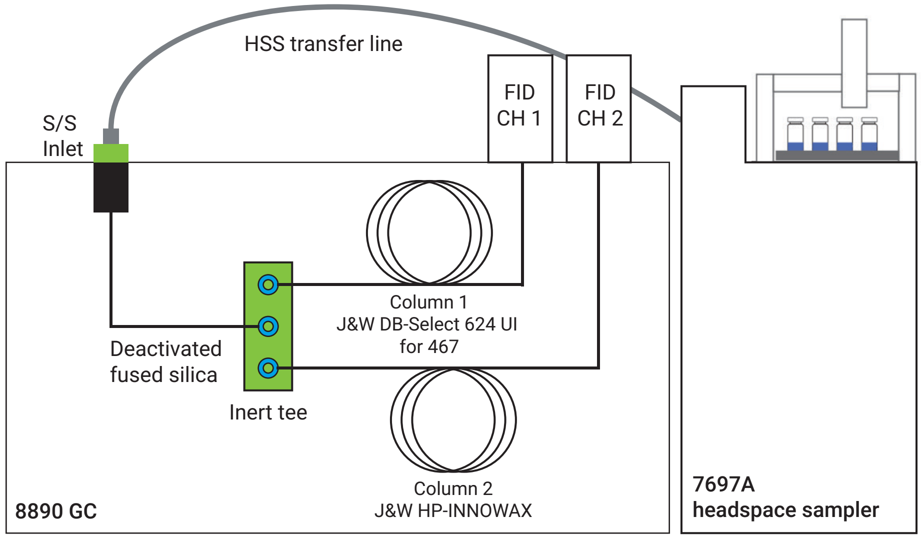


Figure 1. Experimental setup using a dual-column, dual-FID configuration for the analysis of USP <467> residual solvents.

Consumables

Table 1. Consumables and part numbers.

Consumable	Description
Vials	10-mL Clear crimp top headspace vials (p/n 5190–2285)
Septa	Advanced Green nonstick inlet septa (p/n 5183–4759-100)
Splitter	Inert tee for capillary flow technology (p/n G3184-60065)
Ferrules	Short graphite for 0.1 to 0.32 mm columns, 10/pk (p/n 5080-8853) UltiMetal Plus flexible metal, for 0.32 mm fused silica tubing, 10/pk (p/n G3188-27502)
Inlet liner	2 mm, Splitless, straight, deactivated (p/n 5181–8818)
Headspace transfer line/pre-CFT column	Deactivated Fused Silica, 30 m × 0.25 mm id × 0.35 mm od (p/n 160-2255-30)
Column 1	J&W DB-Select 624 UI for 467, 30 m × 0.32 mm, 1.8 µm (p/n 123-0334UI)
Column 2	J&W HP-INNOWax, 30 m × 0.32 mm, 0.25 µm (p/n 19091N-113I)

Sample preparation

Sample preparation for the residual solvent samples was performed according to the USP <467> protocol.

Three stock solutions of residual solvents in DMSO were used:

- Residual Solvent Revised Method <467> Class 1 (p/n 5190-0490)
- Residual Solvent Revised Method <467> Class 2A (p/n 5190-0492)
- Residual Solvent Revised Method <467> Class 2B (p/n 5190-0491)

The sample preparation procedures for each of the three classes are listed below:

Class 1 solvents

1. One milliliter of stock solution vial plus 9 mL of DMSO diluted to 100 mL with water
2. One milliliter from step 1 diluted to 100 mL with water
3. Ten milliliters from step 2 diluted to 100 mL with water
4. One milliliter from step 3 with 5 mL of water into headspace vial

Class 2A solvents

1. One milliliter of stock solution vial, diluted to 100 mL with water
2. One milliliter from step 1 with 5 mL of water into headspace vial

Class 2B solvents

1. One milliliter of stock solution vial, diluted to 100 mL with water
2. One milliliter from step 1 with 5 mL of water into headspace vials

Experimental parameters

Table 2. System parameters for the analysis of residual solvents.

GC system parameter	8890 GC
Carrier gas	Helium constant flow mode, 2 mL/min on column 1
Inlet type	Split/splitless
Inlet temperature	140 °C
Mode	Split mode, split ratio 5:1
Oven	40 °C (hold 5 min) to 180 °C at 18 °C/min (hold 3 min)
Column 1 flow	2 mL/min in constant flow mode, column 2 flow controlled by column 1
FID (both channels)	250 °C
Air	400 mL/min
H_2	30 mL/min
Makeup (N_2)	25 mL/min
Headspace parameter	**7697A headspace sampler**
Sample loop	1 mL
Oven temperature	85 °C
Loop temperature	85 °C
Transfer line temperature	100 °C
Vial equilibration time	40 minutes
Injection duration	0.5 minutes
Vial size	10 mL
Vial shaking	On, level 2 (25 shakes/min)
Vial fill mode	Default: flow to pressure
Vial fill pressure	15 psi
Loop ramp rate	20 psi/min
Final loop pressure	0 psi
Loop equilibration time	0.05 minutes
Software	**Agilent OpenLab CDS – Version 2.2**

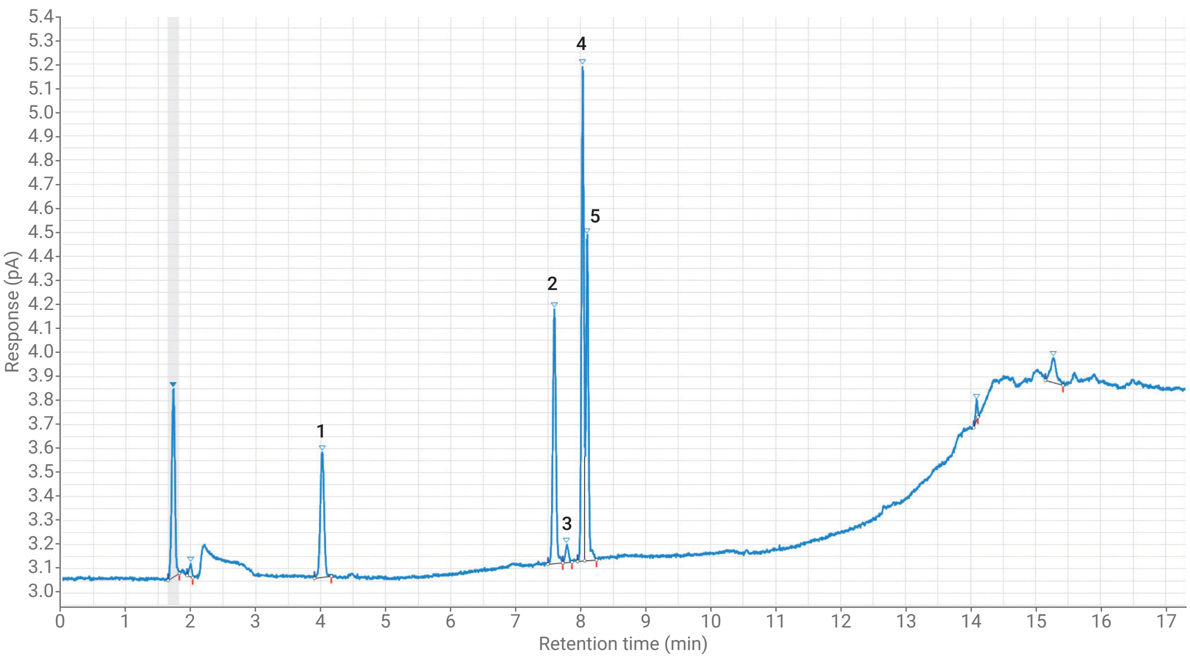
Results and discussion

In addition to showing clear chromatography on both columns for each class of solvents and consistent results across many runs, there are requirements described in USP <467> the analysis must meet.

Figures 2 to 7 illustrate the analysis of classes 1, 2A, and 2B residual solvent mixes on the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax GC columns. Analysis of class 1 solvents meets the signal-to-noise ratio (S/N) and resolution requirements on both the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns.

The area and retention time repeatability measurements (RSD%) were evaluated on a set of 10 headspace vials. Tables 3 to 5 list the RSD% obtained on the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns for class 1, 2A, and 2B residual solvent mixes. The resulting RSD% values were less than 5.0 %, indicating high repeatability and stability of the column, the 7697A headspace sampler, and the 8890 GC/FID system.

Class 1 solvents



Compound	RT
1. 1,1-Dichloroethene	4.018
2. 1,1,1-Trichloroethane	7.590
3. Carbon tetrachloride	7.781
4. Benzene	8.026
5. 1,2-Dichloroethane	8.094

Figure 2. Chromatogram of the USP residual solvents class 1 standard solution resolved on a J&W DB-Select 624 UI for 467 GC column.

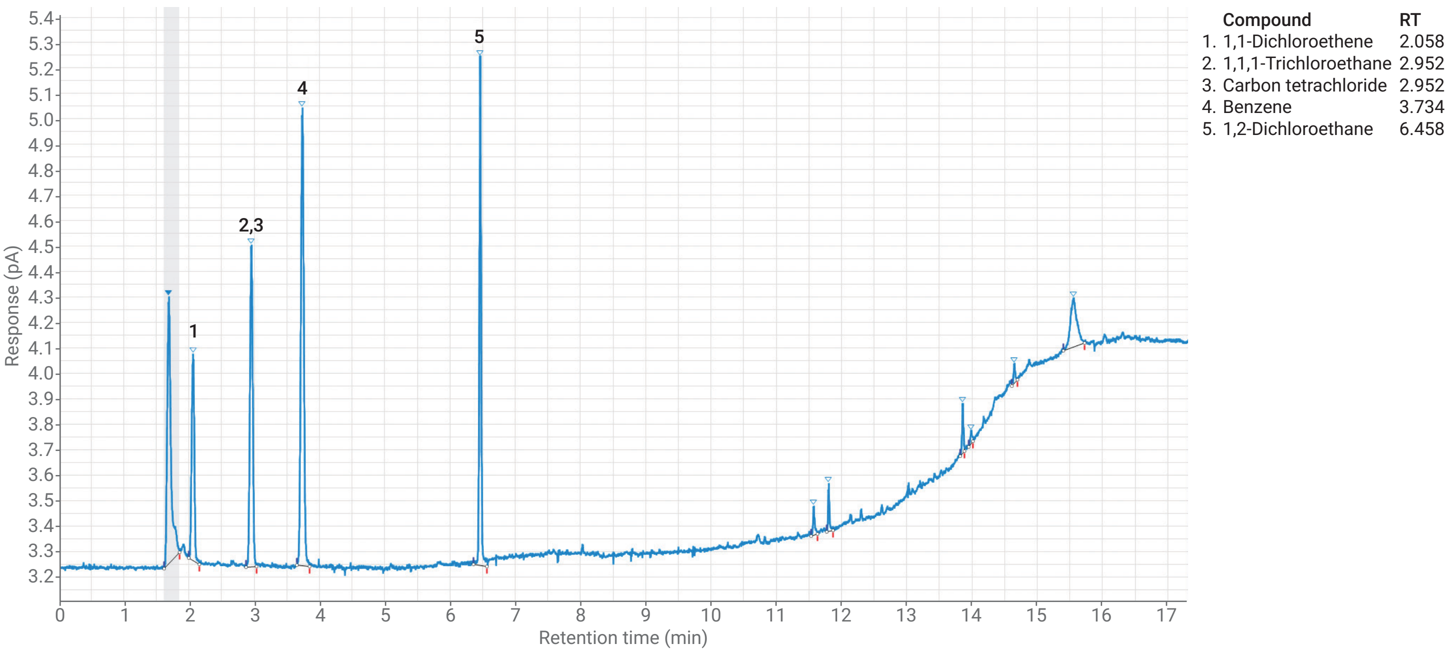
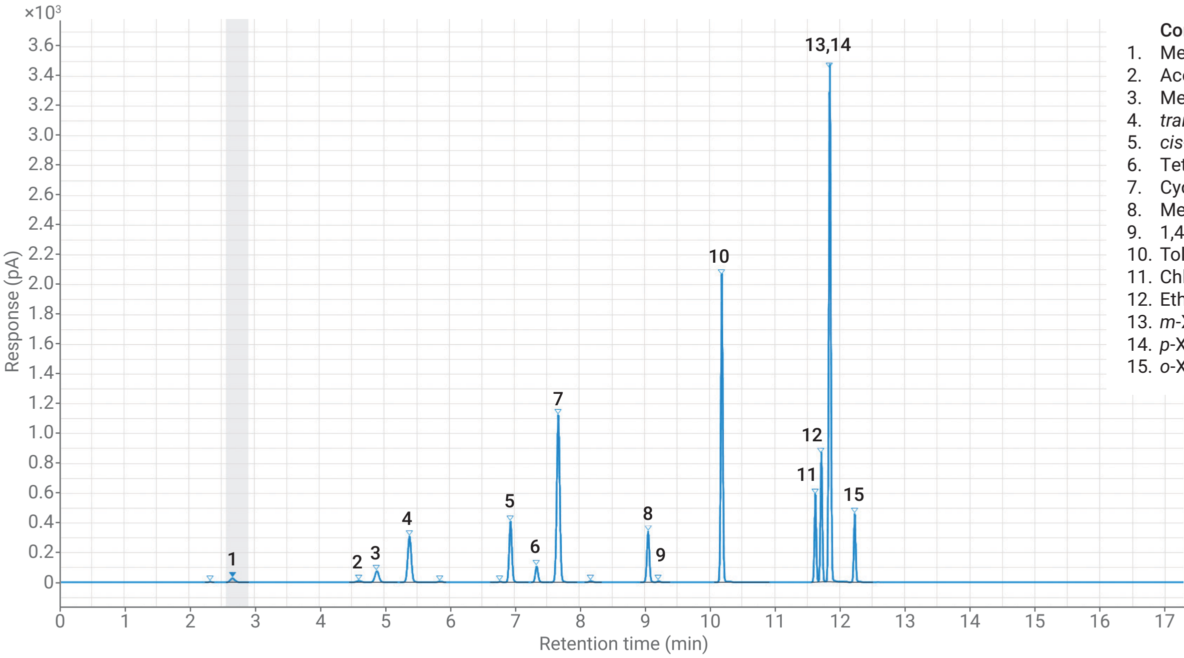


Figure 3. Chromatogram of the USP residual solvents class 1 standard solution resolved on a J&W HP-INNOWax column.

Table 3. Repeatability (n = 10) for class 1 residual solvents obtained on the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns.

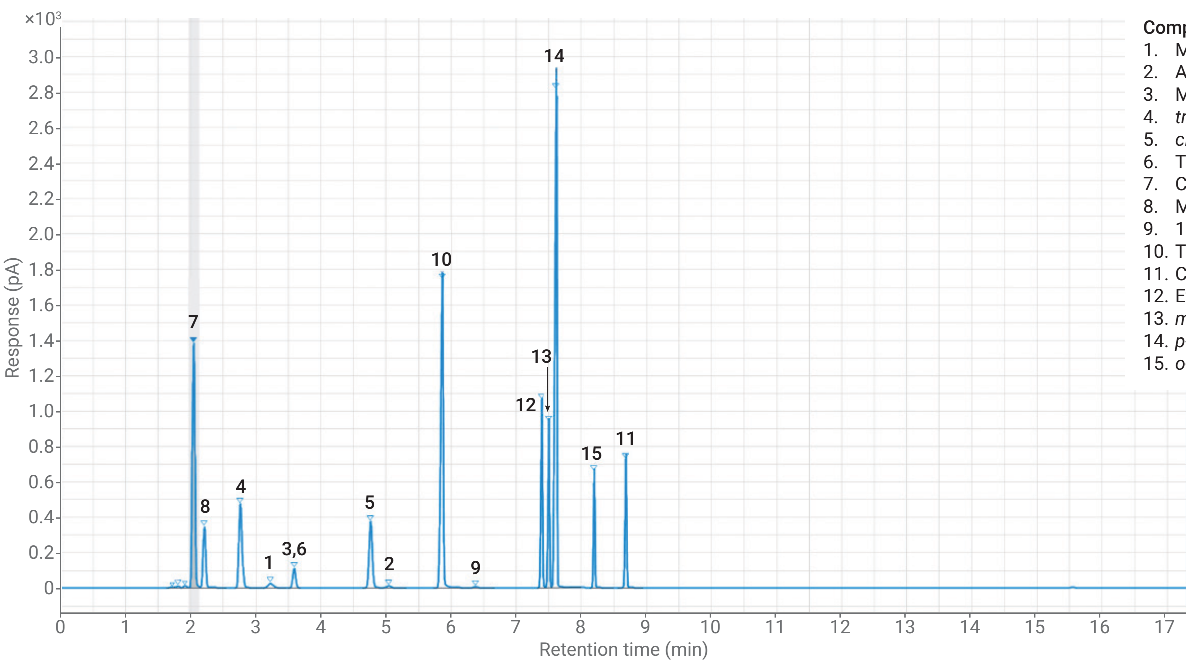
Compound	Area RSD (%) on J&W DB-Select 624 UI for 467	RT RSD (%) on J&W DB-Select 624 UI for 467	Area RSD (%) on J&W HP-INNOWax	RT RSD (%) on J&W HP-INNOWax
1,1-Dichloroethene	2.8	0.31	4.2	0.092
1,1,1-Trichloroethane	3.7	1.4	3.61	0.057
Carbon tetrachloride	2.9	0.060	Coelutes with 1,1,1-trichloroethane	Coelutes with 1,1,1-trichloroethane
Benzene	3.6	0.0050	4.9	0.021
1,2-Dichloroethane	3.2	0.059	3.2	0.018

Class 2A solvents



Compound	RT
1. Methanol	2.665
2. Acetonitrile	4.608
3. Methylene chloride	4.882
4. *trans*-1,2-Dichloroethene	5.384
5. *cis*-1,2-Dichloroethene	6.935
6. Tetrahydrofuran	7.337
7. Cyclohexane	7.670
8. Methylcyclohexane	9.051
9. 1,4-Dioxane	9.211
10. Toluene	10.183
11. Chlorobenzene	11.621
12. Ethylbenzene	11.714
13. *m*-Xylene	11.842
14. *p*-Xylene	11.842
15. *o*-Xylene	12.226

Figure 4. Chromatogram of the USP residual solvents class 2A standard solution resolved on a J&W DB-Select 624 UI for 467 GC column.



Compound	RT
1. Methanol	3.222
2. Acetonitrile	5.039
3. Methylene chloride	3.585
4. *trans*-1,2-Dichloroethene	2.759
5. *cis*-1,2-Dichloroethene	4.760
6. Tetrahydrofuran	3.585
7. Cyclohexane	2.042
8. Methylcyclohexane	2.207
9. 1,4-Dioxane	6.369
10. Toluene	6.859
11. Chlorobenzene	8.679
12. Ethylbenzene	7.368
13. *m*-Xylene	7.498
14. *p*-Xylene	7.609
15. *o*-Xylene	8.193

Figure 5. Chromatogram of the USP residual solvents class 2A standard solution resolved on a J&W HP-INNOWax column.

Table 4. Repeatability (n = 10) for class 2A residual solvents obtained on the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns.

Compound	Area RSD (%) on J&W DB-Select 624 UI for 467	RT RSD (%) on J&W DB-Select 624 UI for 467	Area RSD (%) on J&W HP-INNOWax	RT RSD (%) on J&W HP-INNOWax
Methanol	1.9	0.36	2.0	0.41
Acetonitrile	1.6	0.078	2.4	0.034
Methylene chloride	3.8	0.029	4.1	0.034
trans-1,2-Dichloroethene	4.9	0.031	4.5	0.039
cis-1,2-Dichloroethene	4.3	0.0092	4.3	0.039
Tetrahydrofuran	2.3	0.029	Coelutes with methylene chloride	Coelutes with methylene chloride
Cyclohexane	4.1	0.0091	4.2	0.045
Methylcyclohexane	4.5	0.0059	4.5	0.046
1,4-Dioxane	1.7	0.012	2.4	0.039
Toluene	4.4	0.0053	4.3	0.034
Chlorobenzene	4.1	0.0055	4.1	0.32
Ethylbenzene	4.4	0.0057	4.5	0.04
m-Xylene	4.4	0.0056	4.7	0.026
p-Xylene	Coelutes with *m*-xylene	Coelutes with *m*-xylene	4.4	0.016
o-Xylene	4.1	0.0054	4.1	0.31

Class 2B solvents

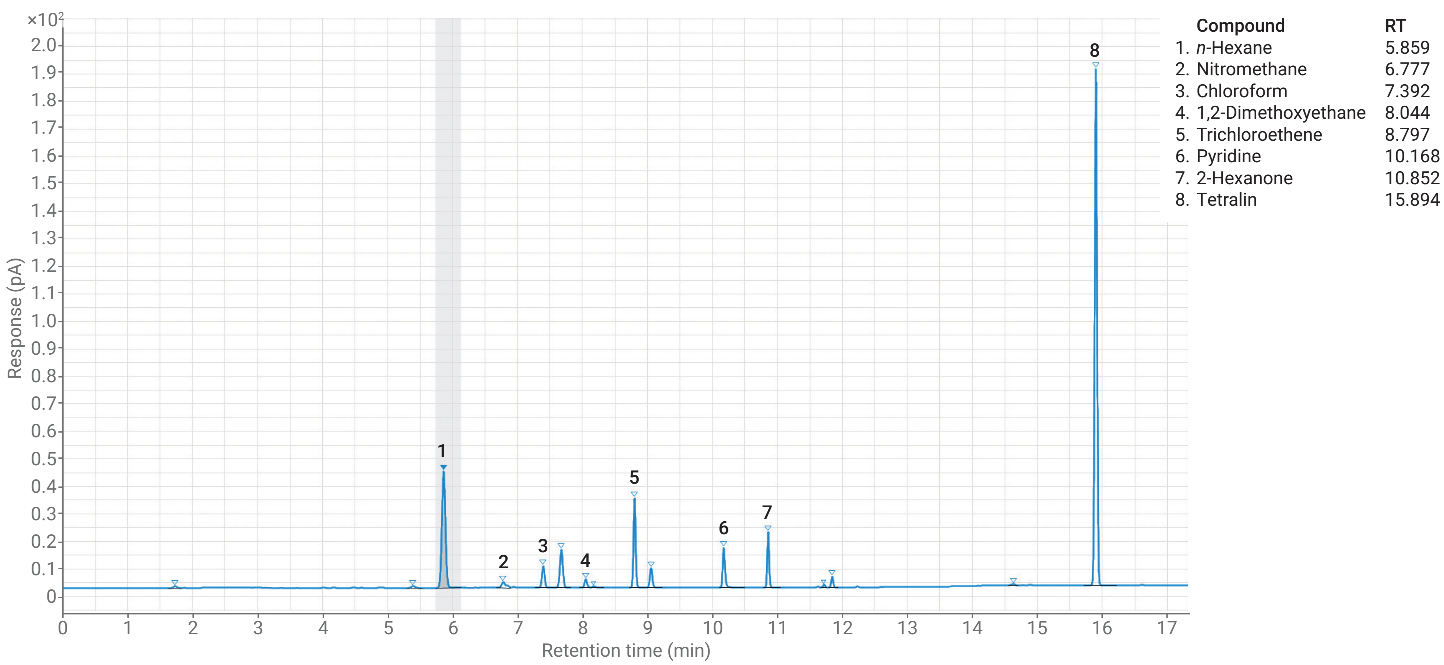


Figure 6. Chromatogram of the USP residual solvents class 2B standard solution resolved on a J&W DB-Select 624 UI for 467 GC column.

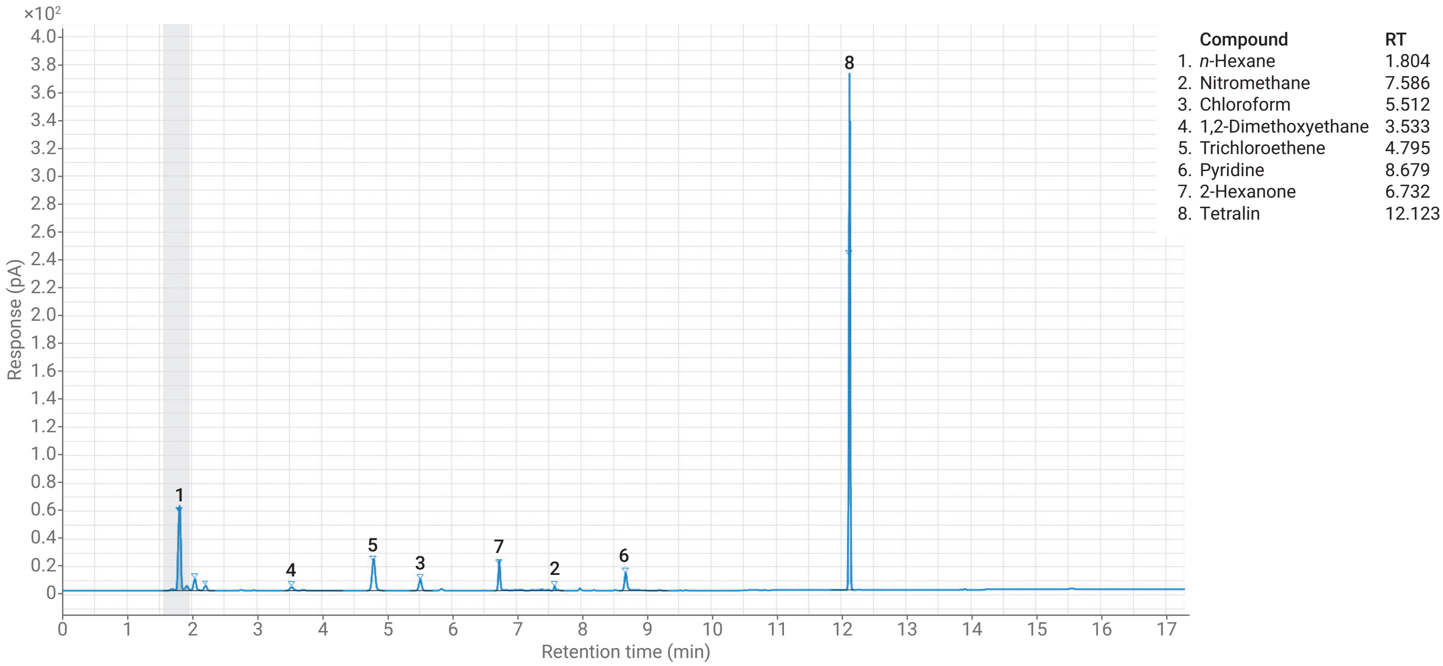


Figure 7. Chromatogram of the USP residual solvents class 2B standard solution resolved on a J&W HP-INNOWax GC column.

Conclusion

The 8890 GC system, equipped with a 7697A headspace sampler and inert tee, provides an excellent method for separating, identifying, and quantifying all of the relevant residual solvents outlined by USP <467>. Beyond the expected coelutions, the peaks in all three classes are well resolved from each other, showing sufficient S/Ns, and can be quantified repeatably.

Table 5. Repeatability (n = 10) for class 2B residual solvents obtained on the J&W DB-Select 624 UI for 467 and J&W HP-INNOWax columns.

Compound	Area RSD (%) on J&W DB-Select 624 UI for 467	RT RSD (%) on J&W DB-Select 624 UI for 467	Area RSD (%) on J&W HP-INNOWax	RT RSD (%) on J&W HP-INNOWax
n-Hexane	1.5	0.052	2.9	0.17
Nitromethane	1.8	0.031	1.8	0.014
Chloroform	4.4	0.0081	4.4	0.014
1,2-Dimethoxyethane	1.9	0.031	2.1	0.086
Trichloroethene	4.7	0.0061	4.9	0.0019
Pyridine	3.3	0.015	3.2	0.085
2-Hexanone	2.8	0.0077	2.8	0.015
Tetralin	3.7	0.0052	3.8	0.085

Reference

1. USP 32-NF 27, General Chapter USP <467> Organic volatile impurities, United States Pharmacopeia. Pharmacopoeia Convention Inc., Rockville, MD, USA.

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