Residual Solvents Analysis for the Pharmaceutical Industry Using the Agilent 8697 Headspace Sampler and 8850 GC-FID System

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Abstract

The manufacturing process for active pharmaceutical ingredients (APIs) may contribute to residual solvents remaining in the final product. Due to regulatory requirements, producers need to monitor and control the levels of residual solvents. In this work, an Agilent 8850 gas chromatography (GC) system coupled with an Agilent 8697 headspace sampler was applied to the residual solvents analysis following the USP Method <467>. The system performance was verified in terms of detectability, resolution, qualification accuracy, and quantitation precision using both helium and hydrogen carrier gas.

Introduction

In the pharmaceutical industry, residual solvents are organic volatile components used in the synthesis of drug substances and excipients. Production solvents do not have therapeutic benefits and are used for increasing the yield or determining characteristics such as crystal form, purity, and solubility. Solvents should be removed as completely as possible to ensure that the products conform to regulatory requirements as specified in ingredient/product specifications, quality-based requirements, and good manufacturing practices. The solvents used in the pharmaceutical industry can be divided into three classes. For the specific solvent in each class, ICH Q3C defines its general acceptable amount in pharmaceutical drug products and dietary supplement products.[1] USP Method <467> describes the procedure for analyzing residual solvents.[2] All Class 1 and the majority of Class 2 solvents can be identified and confirmed, and a concentration limit test can be applied on two GC columns with complementary stationary phases.

As a mature analytical technique, GC is widely used in the off-line or at-line process control environment for monitoring residual solvents in intermediates, APIs, or excipients. To monitor the manufacturing process, a single GC unit is typically assigned to a specific analysis. The samples analyzed by this dedicated GC are sourced from an established manufacturing line and exhibit known properties. Employing this strategy of a dedicated GC minimizes the likelihood of GC damage when compared to scenarios where one GC is required to handle diverse samples from various processes. Consequently, this "one GC to one method/one product" approach ensures the manufacturing line operates more smoothly. Increasing product yield and establishing new manufacturing lines are essential, but the number of dedicated GC units that can fit into a confined lab space is limited. The compact size of the 8850 GC can help alleviate this issue. This innovative GC system has evolved from the legacy design of the Agilent 6850 GC and incorporates state-of-the-art architectural design from the Agilent 8890 platform. The 8850 GC stands out due to its compact size (single-channel configuration, accommodating one inlet, one detector, and one column), swift heating and cooling, intelligent diagnostic and maintenance features, and superior performance on par with the 8890 GC. These characteristics make the 8850 GC a perfect choice for pharmaceutical process control, which demands prompt feedback from a reliable, robust instrument. In the following study, an 8850 GC coupled with an 8697 headspace sampler was used for residual solvent analysis following USP Method <467> for process control purposes. Procedure A and Procedure B of USP <467> were explored using both hydrogen and helium carrier gasses. The Agilent Method Translator greatly simplifies the process of converting the procedures between helium and hydrogen, and its application is also shown.

Experimental

Instrumental and software

An 8850 GC was configured with a split/splitless inlet (S/SL) and one flame ionization detector (FID), and sampling was performed using an 8697 headspace sampler. The data were collected by Agilent OpenLab CDS version 2.8. The six-sigma noise was used to calculate the signal-to-noise ratio (S/N) for Class 1 solvents.

Chemicals

Headspace-grade dimethyl sulfoxide (DMSO) (99.9%) was purchased from Sigma-Aldrich. Ultra pure water was collected from a Milli-Q EQ 7000 Ultrapure Water Purification System. Residuals solvent standards were obtained from Agilent for Class 1 (part number 5190-0490), Class 2A (part number 5190-0492), and Class 2B (part number 5190-0513) solvents. Four single standards of methyl isobutyl ketone (MIBK), cyclopentyl methyl ether (CPME), tert-butanol (TBA), and cumene were purchased from Alta Scientific Co. Ltd.

Sample preparation

Sample preparation for the residual solvent samples was performed according to the USP <467> protocol (Figure 1). Three solvent standard mixtures were diluted to form the standard solution at the concentration limit of each solvent. MIBK, TBA, CPME, and cumene were not included in the initial Class 1 and Class 2 standard mixture. They were prepared at a certain concentration in DMSO and spiked into the diluted Class 2A solution to their limit concentrations.

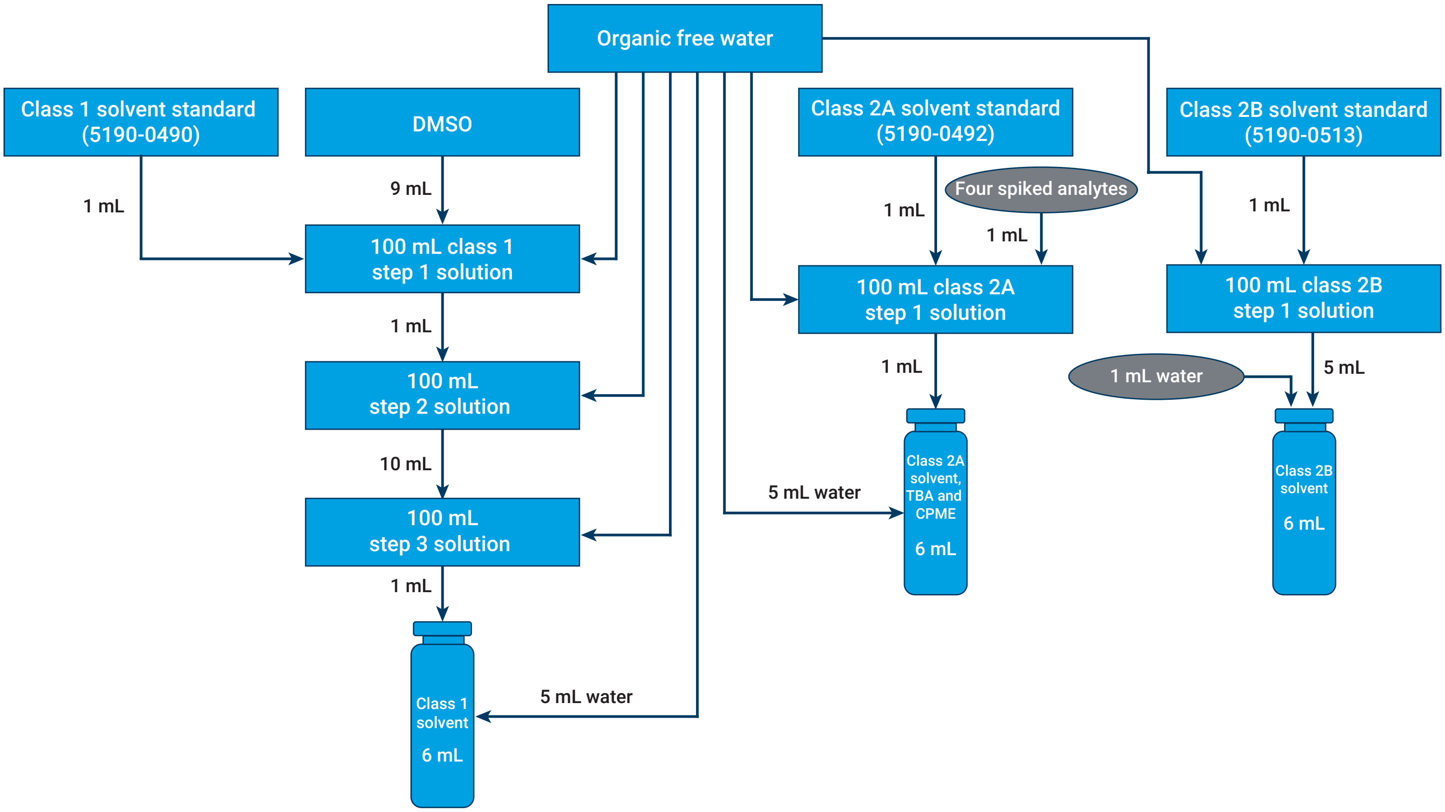


Figure 1. Test standard preparation of Class 1 and Class 2 solvents according to USP Method <467>.

Instrument conditions and consumables

Table 1. The analytical parameters of the Agilent 8850 GC and Agilent 8697 headspace sampler.

Parameter	Value
Agilent 8850 GC	
Inlet	140 °C, split mode
Inlet Liner	2 mm, splitless, straight, deactivated (p/n 5181-8818)
Split Ratio	10:1
Carrier Gas	He and H_2
Column Flow Rate	Constant flow mode He: 2 mL/min; H_2: 2.5 mL/min
Column 1 for Procedure A	Agilent J&W DB-Select 624 UI for 467, 30 m × 0.32 mm, 1.8 µm (p/n 123-0334UIE)
Column 2 for Procedure B	Agilent J&W DB-WAX UI, 30 m × 0.32 mm, 0.25 µm (p/n 123-7032UIE)
Oven Program	He: 40 °C (hold 5 min) to 180 °C at 18 °C/min (hold 5 min) H_2: 40 °C (hold 3.6 min) to 180 °C at 25 °C/min (hold 3.6 min)
FID Temperature	250 °C
Air	400 mL/min
H_2	30 mL/min
Makeup (N_2)	25 mL/min
Data Rate	10 Hz

Parameter	Value
Agilent 8697 Headspace Sampler	
Sample Loop	1 mL
Headspace Oven Temperature	85 °C
Loop Temperature	85 °C
Transfer Line Temperature	100 °C
Vial Equilibration Time	40 min
Vial Size	20 mL
Vial Shaking	Level 2 (25 shakes/min)
Vial Fill Mode	Default
Vial Fill Pressure	15 psi
Pressurization Gas	Nitrogen
Pressure Equilibration Time	0.1 min
Loop Ramp Rate	20 psi/min
Final Loop Pressure	4 psi
Loop Equilibration Time	0.05 min

Results and discussion

The 8697 headspace sampler/8850 GC system performance for residual solvents analysis was verified according to the identification procedures and requirements described in USP <467> standard. Procedure A was performed on G43-type stationary phase. This study used the 5-inch format of the Agilent J&W DB-Select 624 UI for procedure A analysis. A total of 32 solvents were analyzed at their limit concentration. Among them, two solvents (CPME and TBA) were added to the Class 2 solvents list according to ICH Q3C(R8), but they are not yet official in USP <467>. USP <467> requires that in procedure A, if a peak response of any peak in the test sample solution is greater than or equal to a corresponding peak in either the Class 1 or Class 2 standard solution, Procedure B should be performed to verify the identity of the peak. The column stationary phase used in procedure B is different from that used in procedure A for complementary identification purposes. The 5-inch format of the Agilent J&W DB-WAX UI column, a stationary phase similar to G16 as USP <467> recommends, was used for procedure B. The analytical requirements for procedures A and B are as follows:

Procedure A system suitability test:

- The S/N for 1,1,1-trichloroethane in the Class 1 standard solution is no less than 5.
- The S/N of each peak in the Class 1 system suitability solution is no less than 3.
- The resolution between acetonitrile and methylene chloride in the Class 2 mixture A standard solution is no less than 1.0.

Procedure B system suitability test:

- The S/N for benzene in the Class 1 standard solution is no less than 5.
- The S/N of each peak in the Class 1 system suitability solution is no less than 3.
- The resolution between MIBK and *cis*-1,2-dichloroethene in the Class 2 mixture A standard solution is no less than 1.0.

Analysis of Class 1 and Class 2 residual solvents using He carrier gas

Class 1 solvents possess unacceptable toxicities or deleterious environmental effects, and their acceptable limits are the lowest compared to Class 2A and 2B solvents. Figure 2 presents the chromatograms of Class 1 solvents in procedure A and procedure B. The corresponding S/N ratios of 1,1,1-trichloroethane, benzene, and carbon tetrachloride (the lowest-response compound among Class 1 solvents) are listed in the chromatograms.

For Class 2 solvents analysis, the resolution between acetonitrile and methylene chloride is 3.3, greater than 1.0 of the resolution threshold for solvent screening. MIBK/CPME and *m*-xylene/*p*-xylene are two compound pairs coeluting in procedure A that are well separated in procedure B (Figure 3). The resolution of MIBK and *cis*-1,2-dichloroethene in procedure B is greater than 4.0. Acetonitrile eluted between MIBK and *cis*-1,2-dichloroethene in procedure B, with the acetonitrile peak right before the MIBK peak. USP <467> also requires that in the target solvent analysis the resolution between each pair of solvents should be no less than 1.0; the achieved resolution of acetonitrile and MIBK of 1.9 easily satisfied this requirement.

The response of solvents at the tested limit concentration varied in the chromatograms. Such a response difference is caused by differences in compound partition coefficient constants between water and air, the specific response factor of each solvent, and the individual limit concentration. Among the test solvents, methanol and acetonitrile have the high partition coefficient constants (K), which resulted in less evaporation into the headspace gas phase for FID detection. Accordingly, their peaks are quite small. The response factor of nitromethane is low, so its peak area is also very small. The solvents with a lower response at the limit concentration tend to give bigger area %RSD compared to those showing a higher response, which are shown in the method precision results.

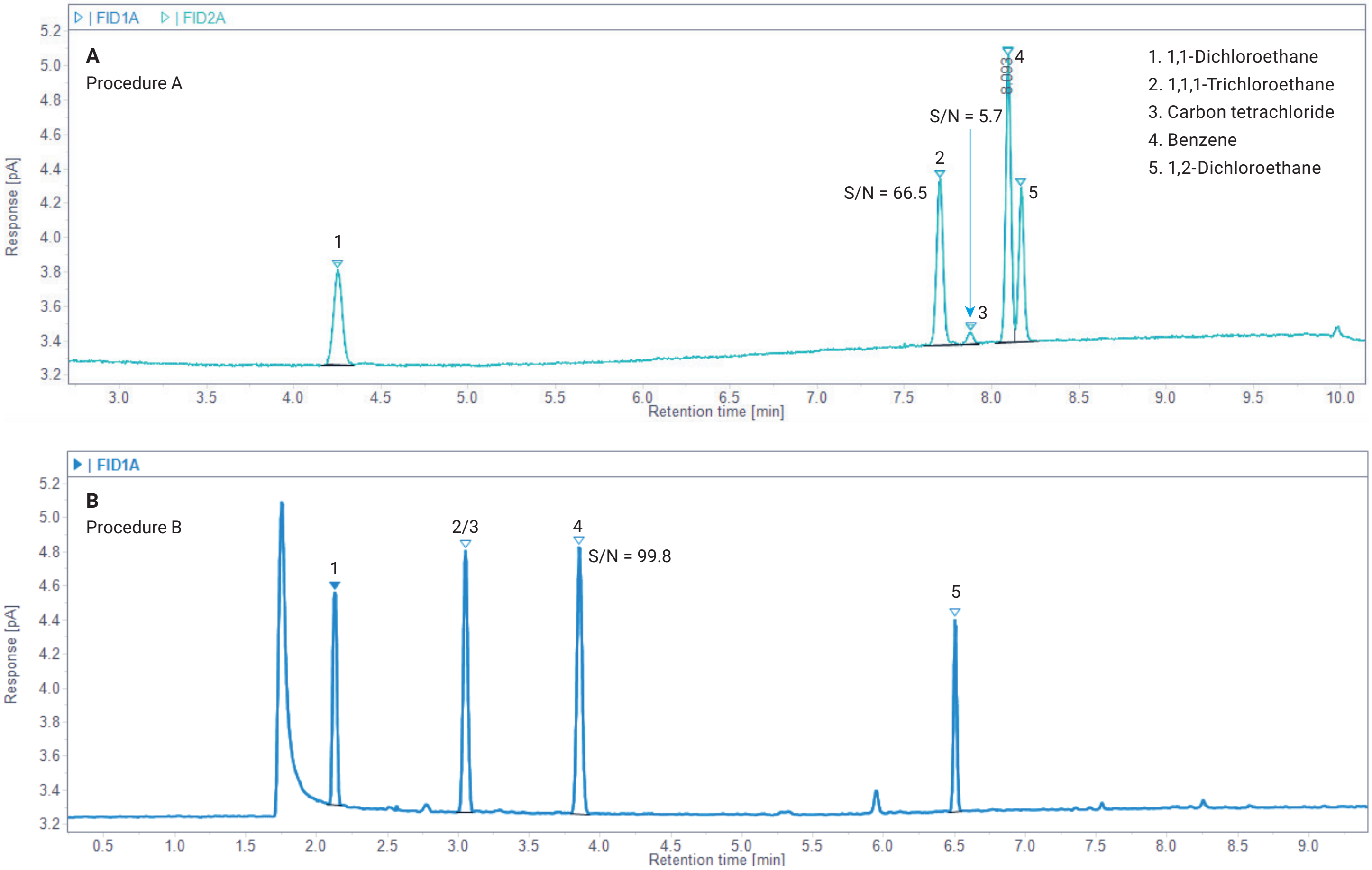


Figure 2. Class 1 solvents identified in procedures A and B using helium.

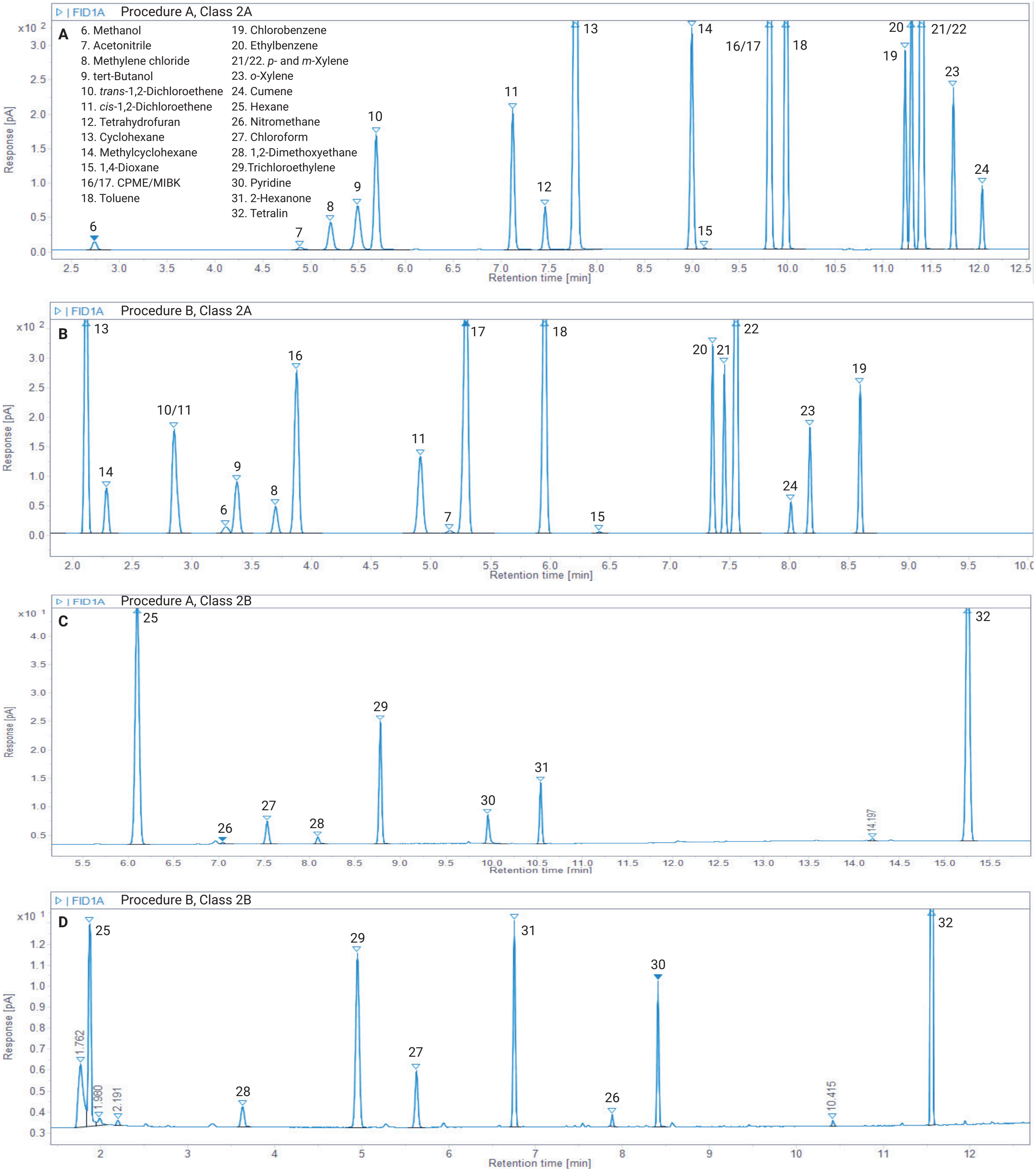


Figure 3. Class 2A and Class 2B solvents identified in procedure A (Agilent DB-624 select UI 467 column) and B (Agilent DB-WAX UI column) using helium carrier gas.

The precision of the helium method was evaluated based on six consecutive injections of Class 1 and Class 2 standards at limit concentrations in procedures A and B. The area %RSD ranged from 0.65% to 3.46% with an average of 1.78% in procedure A, and 0.60% to 3.30% with an average of 1.85% in procedure B (Figure 4). Four compounds showed an area %RSD greater than 3.0%, including carbon tetrachloride (3.46%) in procedure A, and acetonitrile (3.18%), nitromethane (3.11%), and pyridine (3.30%) in procedure B. Carbon tetrachloride, acetonitrile, and nitromethane showed low absolute response, which made their response %RSD bigger than other components. The retention time (RT) precision in procedure A ranged from 0.003% to 0.033% with an average of 0.007%, and 0.006% to 0.036% in procedure B with an average of 0.017% (details in Table 3, Appendix). The excellent RT precision helps ensure the reliable identification (procedure A) and confirmation (procedure B) of detected compounds for all use cases, such as screening tests and limit tests (using either procedure A or procedure B) executed during the manufacturing process.

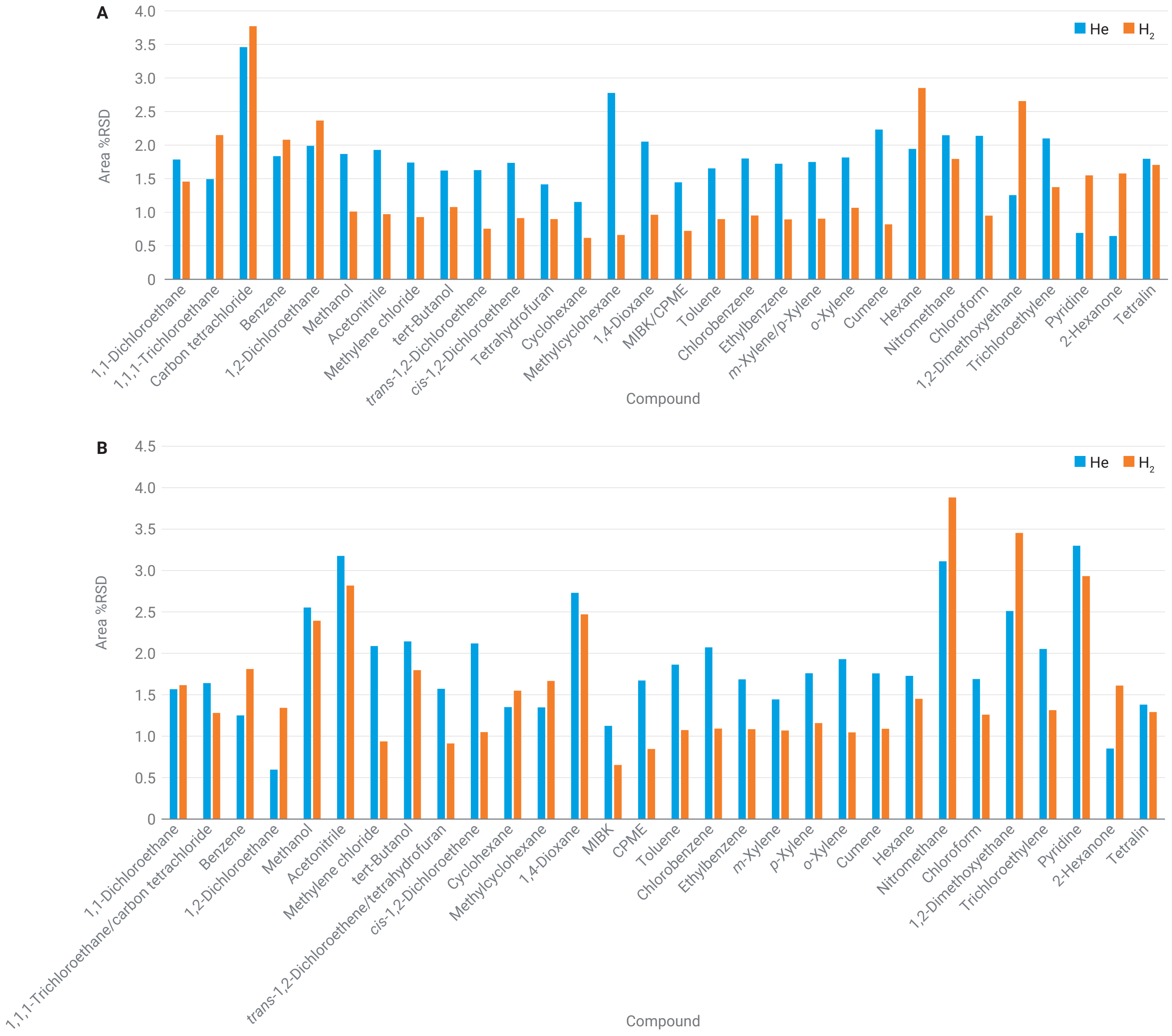
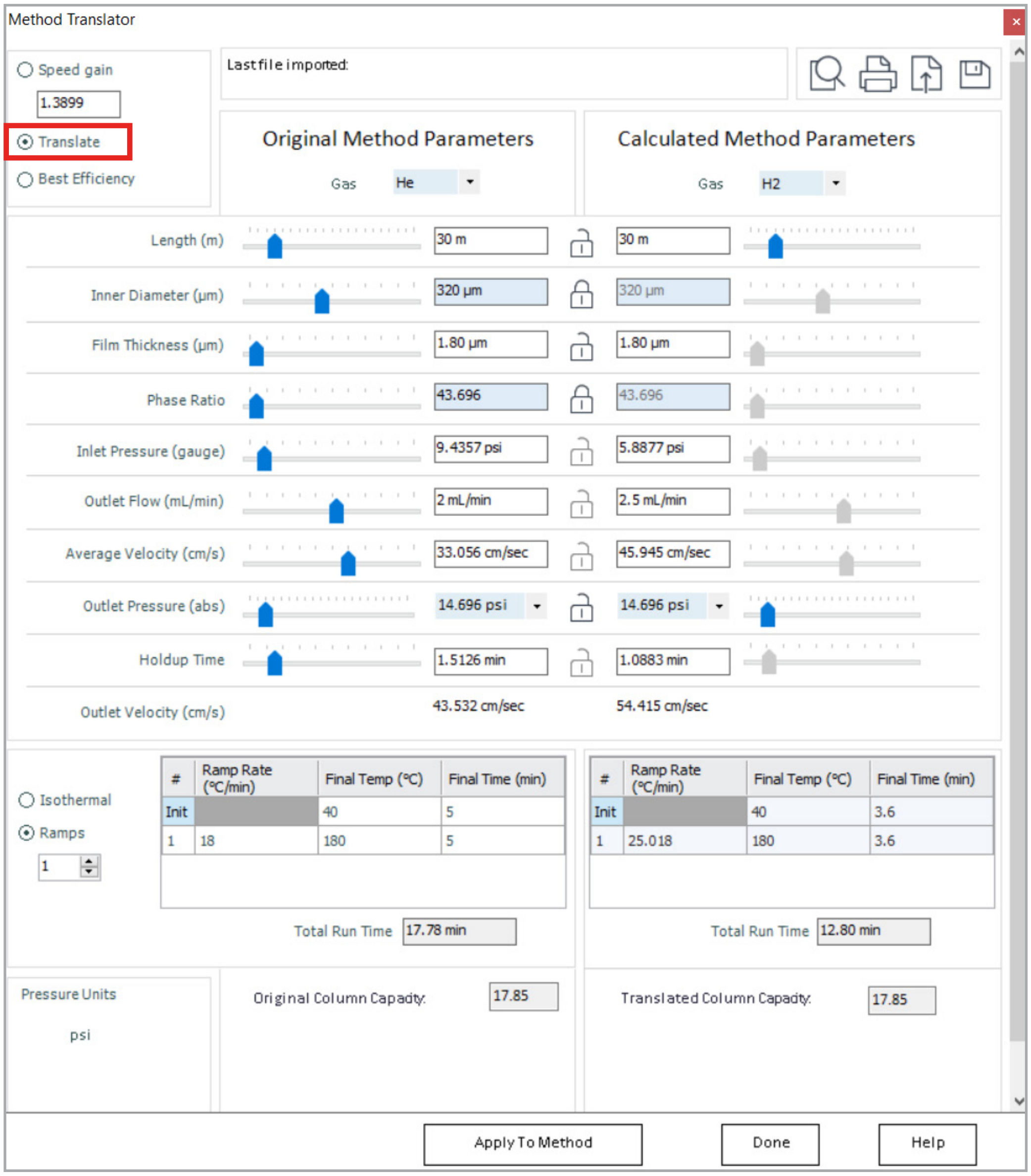


Figure 4. Area precision of Class 1 and Class 2 solvents in procedure A and procedure B using different carrier gas.

Analysis of Class 1 and Class 2 residual solvents using H_2 carrier gas

USP <467> recommends three types of carrier gas in GC separation: He, N_2, and H_2. Helium is most commonly used due to its inertness, purity, and excellent performance; however, helium demand keeps growing, and its supply is unreliable. More GC users are seeking alternative carrier gases. Both nitrogen and hydrogen-based methodologies are developed in different industries. Compared to nitrogen, hydrogen provides good separation without sacrificing analysis speed. A previous application note studied USP <467> residual solvents analysis using nitrogen carrier gas.[3] In this work, the residual solvents analysis based on a hydrogen method was developed. The Method Translator tool was used to translate the He method to an H_2 method. As shown in Figure 5, by selecting the Translate option, the analytical parameters in the He method were converted into the conditions used in the H_2 method, and the analysis speed gain was predicted. The converted method can be used directly or as a starting point for new methods that can be further refined to meet specific analytical requirements. Here, the converted method was applied directly to residual solvents analysis when switching to H_2 carrier gas.



Method Translator

○ Speed gain 1.3899

● Translate

○ Best Efficiency

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	Original Method Parameters	Calculated Method Parameters
Gas	He	H2
Length (m)	30 m	30 m
Inner Diameter (µm)	320 µm	320 µm
Film Thickness (µm)	1.80 µm	1.80 µm
Phase Ratio	43.696	43.696
Inlet Pressure (gauge)	9.4357 psi	5.8877 psi
Outlet Flow (mL/min)	2 mL/min	2.5 mL/min
Average Velocity (cm/s)	33.056 cm/sec	45.945 cm/sec
Outlet Pressure (abs)	14.696 psi	14.696 psi
Holdup Time	1.5126 min	1.0883 min
Outlet Velocity (cm/s)	43.532 cm/sec	54.415 cm/sec

○ Isothermal

● Ramps 1

#	Ramp Rate (°C/min)	Final Temp (°C)	Final Time (min)
Init		40	5
1	18	180	5

Total Run Time 17.78 min

#	Ramp Rate (°C/min)	Final Temp (°C)	Final Time (min)
Init		40	3.6
1	25.018	180	3.6

Total Run Time 12.80 min

Pressure Units psi

Original Column Capacity: 17.85

Translated Column Capacity: 17.85

Figure 5. Method Translator conversion of a He method to an H_2 method.

The resulting chromatograms from converting to H_2 carrier gas are shown in Figures 6 and 7. In both procedures A and B, the RT ratio of each solvent between the He and H_2 methods is from 71% to 74% (Table 2), which is consistent with the speed gain of 1.39 predicted by the Method Translator tool.

Table 2. Retention time ratio of each solvent using the He and H_2 methods.

	He	H_2		He	H_2	
Compound Name	**RT on DB-624/min**	**RT on DB-624/min**	**RT Ratio on DB-624 (%)**	**RT on DB-WAX/min**	**RT on DB-WAX/min**	**RT Ratio on DB-WAX (%)**
1,1-Dichloroethane	4.25	3.114	73.3	2.125	1.566	73.7
1,1,1-Trichloroethane	7.702	5.535	71.9	3.047	2.231	73.2
Carbon Tetrachloride	7.876	5.658	71.8	3.047	2.231	73.2
Benzene	8.094	5.812	71.8	3.85	2.81	73.0
1,2-Dichloroethane	8.168	5.864	71.8	6.501	4.703	72.3
Methanol	2.733	2.033	74.4	3.281	2.402	73.2
Acetonitrile	4.886	3.572	73.1	5.155	3.749	72.7
Methylene Chloride	5.205	3.792	72.9	3.696	2.702	73.1
tert-Butanol	5.489	3.982	72.5	3.372	2.467	73.2
trans-1,2-Dichloroethene	5.683	4.123	72.5	2.847	2.09	73.4
cis-1,2-Dichloroethene	7.114	5.124	72.0	4.908	3.573	72.8
Tetrahydrofuran	7.454	5.362	71.9	2.847	2.09	73.4
Cyclohexane	7.771	5.586	71.9	2.111	1.556	73.7
Methylcyclohexane	8.991	6.445	71.7	2.281	1.679	73.6
1,4-Dioxane	9.126	6.541	71.7	6.407	4.632	72.3
MIBK	9.806	7.021	71.6	5.291	3.836	72.5
CPME	9.806	7.021	71.6	3.872	2.825	73.0
Toluene	9.98	7.144	71.6	5.948	4.304	72.4
Chlorobenzene	11.228	8.029	71.5	8.586	6.18	72.0
Ethylbenzene	11.295	8.076	71.5	7.354	5.309	72.2
m-Xylene	11.399	8.15	71.5	8.006	5.77	72.1
p-Xylene	11.399	8.15	71.5	7.452	5.378	72.2
o-Xylene	11.735	8.388	71.5	8.166	5.882	72.0
Cumene	12.037	8.602	71.5	7.55	5.446	72.1
Hexane	6.1	4.409	72.3	1.87	1.383	74.0
Nitromethane	7.035	5.067	72.0	7.878	5.685	72.2
Chloroform	7.527	5.413	71.9	5.626	4.079	72.5
1,2-Dimethoxyethane	8.08	5.801	71.8	3.626	2.65	73.1
Trichloroethylene	8.773	6.29	71.7	4.948	3.601	72.8
Pyridine	9.948	7.12	71.6	8.404	6.054	72.0
2-Hexanone	10.539	7.54	71.5	6.751	4.879	72.3
Tetralin	15.252	10.85	71.1	11.552	8.276	71.6

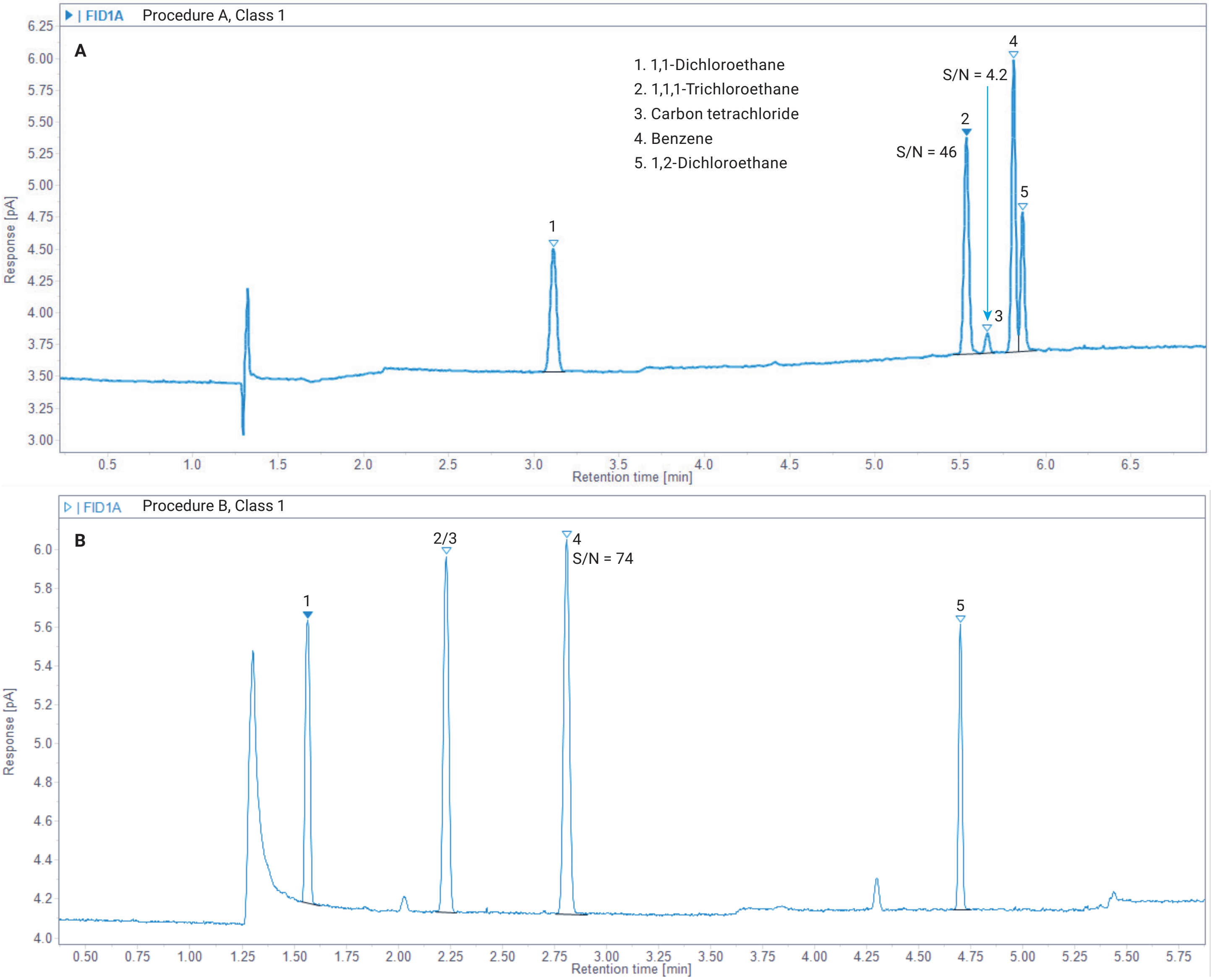

Figure 6. Class 1 solvents identified in procedures A and B using hydrogen carrier gas.

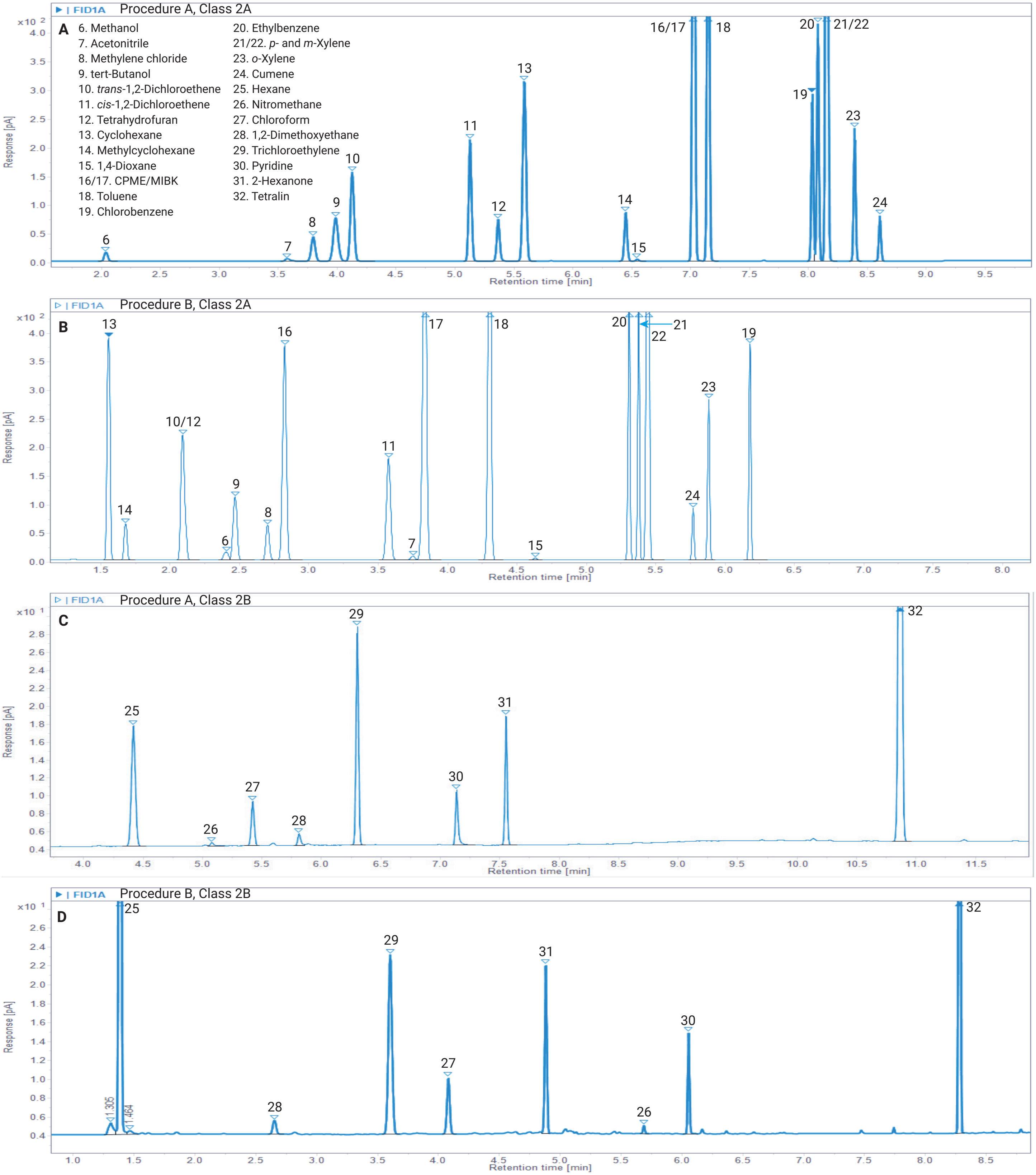

Figure 7. Class 2A and Class 2B solvents identified in procedure A (Agilent DB-624 select UI 467 column) and B (Agilent DB-WAX UI column) using hydrogen carrier gas.

The detectability and separation capability in procedure A and B using H_2 carrier gas met the system suitability requirements in terms of Class 1 solvent S/N ratio and resolution between key Class 2 solvents. The S/Ns for 1,1,1-trichloroethane, benzene, and carbon tetrachloride (listed in the chromatograms) were comparable to those obtained using the He method. The resolution (RS) of acetonitrile and MIBK on a DB-WAX column using H_2 (procedure B) is 1.6, also comparable with the RS of 1.9 in the He method (Figure 8). The method precision was evaluated using the same assessment approach for the He method by running six consecutive analyses of Class 1 and Class 2 solvents at limit concentration. The RT precision of the H_2 method in procedure A is slightly worse than the He method for the early eluted compounds such as methanol, acetonitrile, and tert-butanol. Considering that the RTs for these three components are quite short (less than 4.0 minutes in the H_2 method), even though their RT %RSD between 0.03% and 0.07% is a little higher than other solvents, the results are still sufficient for accurate qualification. The area precision of the H_2 method is comparable to that of the He method, with most solvents having area %RSD less than 3.5%, ensuring the solvent limit test accuracy with a high level of confidence. Detailed H_2 method precision results are shown in Table 3 in the Appendix.

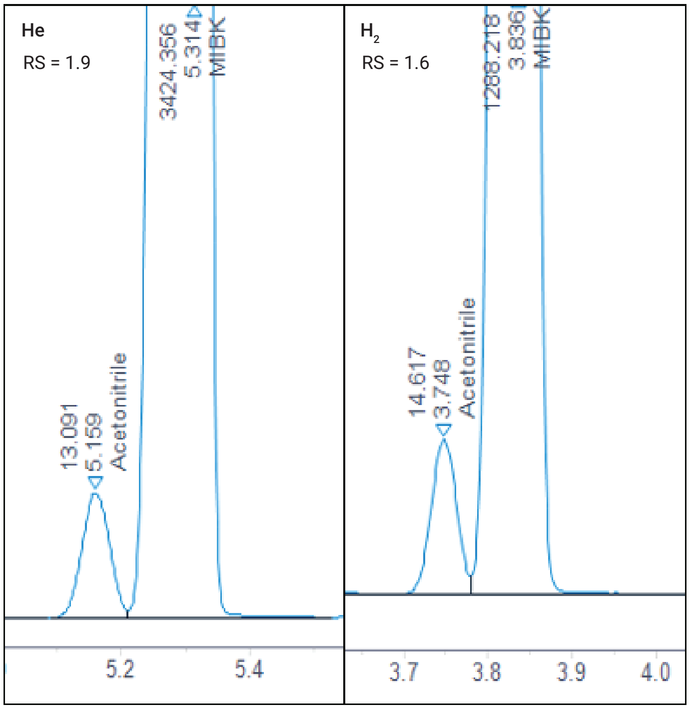

Figure 8. USP resolution between acetonitrile and MIBK on an Agilent DB-WAX UI column (procedure B) using helium and hydrogen carrier gas.

Two-dimensional RT distribution of Class 1 and Class 2 solvents on DB-624 and DB-WAX columns

To demonstrate the complete resolution of 32 target solvents on DB-624 select and DB-WAX columns more clearly, a two-dimensional (2D) RT map was plotted using the RT on the DB-624 column as the horizontal axis and the RT on the DB-WAX column as the vertical axis. The 2D RT map was plotted for He and H_2 methods (Figures 9A and 9B). Each spot represents a solvent. No overlap means the solvents are well separated by the complementary qualification in procedures A and B. The same distribution pattern between two plots means that when using H_2 carrier gas, there is no change in selectivity and the system resolution is kept at a maximum level.

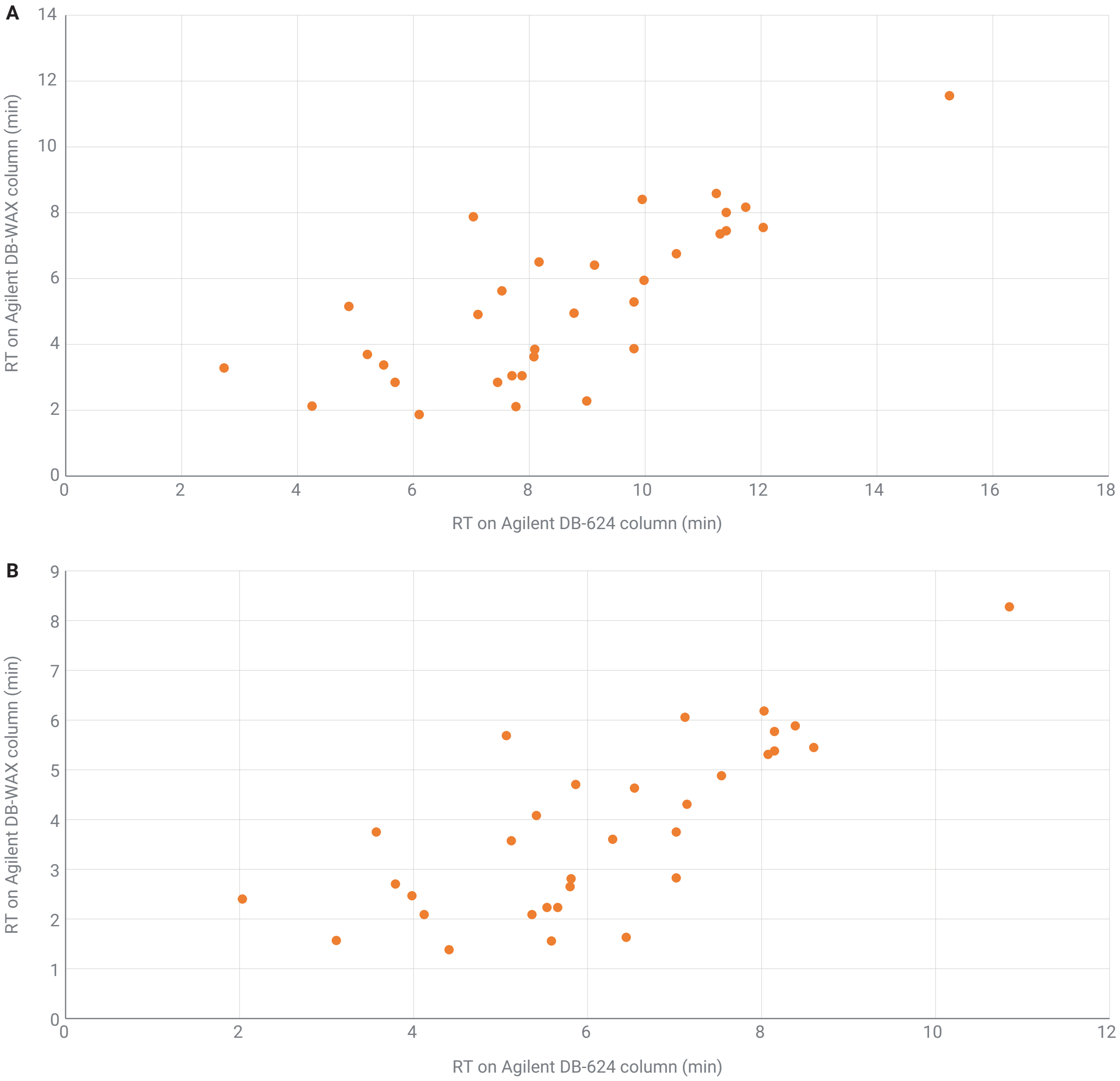

Figure 9. Two-dimensional RT map of 32 solvents based on procedure A and procedure B separations obtained using He (A) and H_2 (B) methods.

Conclusion

In this application note, an Agilent 8850 GC was coupled with an Agilent 8697 headspace sampler for residual solvents analysis following the USP <467> method. Either procedure A or procedure B analysis can be performed by connecting the proper type of column on this system. Two carrier gases, helium and hydrogen, were used for performance evaluation. The H_2 method was developed by converting the He method using the Agilent Method Translator tool. The system performance, including the S/N of Class 1 solvents and resolution of key probe compounds in Class 2 solvents, met and exceeded the system suitability test requirements in USP <467>. The retention time and area precision achieved in both methods are excellent and consistent with each other, which indicates the 8697 HS-8850 GC system can provide reliable identification/confirmation for solvent screening tests and accurate limit tests for target solvents analyzed during process monitoring.

References

1. U.S. FDA. Impurities: Guidance for Residual Solvents Q3C (R8). Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry (**2021**).
2. USP Residual Solvents. 467 Residual Solvents (uspnf.com)
3. Zhang, Y. Analysis of USP Residual Solvents Using the Agilent 8697 Headspace Sampler -XL Tray and Agilent 8890 GC System. *Agilent Technologies application note*, publication number 5994-6020EN, **2023**.

Appendix

Table 3. Method precision using helium and hydrogen carrier gas.

Compounds	Helium Method				Hydrogen Method			
	Agilent DB-624 Select UI		Agilent DB-WAX UI		Agilent DB-624 Select UI		Agilent DB-WAX UI	
	RT %RSD	Area %RSD	RT %RSD	Area %RSD	RT %RSD	Area %RSD	RT %RSD	Area %RSD
1,1-Dichloroethane	0.014	1.786	0.017	1.568	0.024	1.456	0.012	1.617
1,1,1-Trichloroethane	0.008	1.494	0.016	1.641	0.008	2.149	0.01	1.281
Carbon Tetrachloride	0.033	3.46	Coeluted with 1,1,1-trichloroethane		0.011	3.771	Coeluted with 1,1,1-trichloroethane	
Benzene	0.006	1.836	0.026	1.252	0.006	2.081	0.012	1.812
1,2-Dichloroethane	0.005	1.99	0.013	0.597	0.009	2.366	0.016	1.343
Methanol	0.023	1.868	0.034	2.554	0.07	1.009	0.025	2.394
Acetonitrile	0.014	1.929	0.022	3.177	0.041	0.971	0.028	2.818
Methylene Chloride	0.014	1.739	0.02	2.088	0.029	0.928	0.019	0.938
tert-Butanol	0.01	1.621	0.016	2.144	0.038	1.077	0.02	1.798
trans-1,2-Dichloroethene	0.008	1.627	0.015	1.572	0.022	0.754	0.013	0.913
cis-1,2-Dichloroethene	0.005	1.735	0.015	2.12	0.014	0.912	0.023	1.05
Tetrahydrofuran	0.006	1.414	Coeluted with *trans*-1,2-dichloroethene		0.013	0.898	Coeluted with *trans*-1,2-dichloroethene	
Cyclohexane	0.007	1.152	0.009	1.352	0.012	0.617	0.008	1.549
Methylcyclohexane	0.004	2.778	0.011	1.348	0.006	0.662	0.009	1.667
1,4-Dioxane	0.003	2.051	0.011	2.73	0.01	0.963	0.017	2.471
MIBK	0.004	1.446	0.014	1.126	0.006	0.721	0.023	0.653
CPME	Coeluted with MIBK		0.016	1.672	Coeluted with MIBK		0.016	0.846
Toluene	0.003	1.653	0.012	1.864	0.005	0.897	0.017	1.075
Chlorobenzene	0.004	1.801	0.024	2.072	0.004	0.952	0.008	1.091
Ethylbenzene	0.005	1.723	0.006	1.687	0.003	0.893	0.021	1.084
m-Xylene	0.003	1.748	0.032	1.445	0.004	0.903	0.018	1.069
p-Xylene	Coeluted with *m*-xylene		0.006	1.76	Coeluted with *m*-xylene		0.019	1.159
o-Xylene	0.005	1.816	0.025	1.931	0.004	1.067	0.016	1.046
Cumene	0.004	2.232	0.028	1.759	0.003	0.819	0.011	1.09
Hexane	0.01	1.944	0.012	1.729	0.021	2.851	0.022	1.452
Nitromethane	0.009	2.227	0.009	3.111	0.017	1.794	0.019	3.882
Chloroform	0.008	2.138	0.009	1.691	0.011	0.95	0.024	1.26
1,2-Dimethoxyethane	0.009	1.255	0.023	2.511	0.012	2.656	0.033	3.453
Trichloroethylene	0.006	2.1	0.018	2.053	0.006	1.373	0.036	1.315
Pyridine	0.006	0.691	0.035	3.299	0.007	1.55	0.045	2.932
2-Hexanone	0.003	0.646	0.008	0.852	0.007	1.577	0.022	1.611
Tetralin	0.003	1.796	0.006	1.381	0.005	1.706	0.006	1.292

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