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Implementation of USP <467> "Residual Solvents" using a GERSTEL MPS 2 Syringe Based Headspace Autosampler

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Abstract
USP <467> Residual Solvents [1] is a general chapter in the US Pharmacopeia that describes a headspace gas chromatographic method for the determination of residual solvents in pharmaceutical products, active ingredients, and excipients. As originally written, it described parameters used with balanced-pressure or pressure loop based headspace instruments. Recent updates [2] have included parameters for syringe based systems.

Introduction
This application note demonstrates implementation of USP <467> Residual Solvents using the GERSTEL MPS 2 configured as automated headspace sampler. Children's non-aspirin (acetaminophen) suspension liquid was purchased locally and spiked to a level of 2000 µg/g (5 times the acceptable concentration limit) with acetonitrile. This solution was used as the test article.

Experimental

Instrumentation. Analyses were performed on a Model 6890 gas chromatograph equipped with a flame ionization detector (FID) (Agilent Technologies), PTV inlet (CIS 4, Gerstel) and MPS 2 robotic sampler with a 2.5 mL heated headspace syringe (Gerstel).

Analysis conditions.

Headspace:	80°C (sample)
	90°C (syringe)
CIS 4:	Split; 140°C
Column:	30 m ZB-624 (Phenomenex®)
	d_i = 0.32 mm, d_f = 1.8 um
	30 m ZB-WAXplus (Phenomenex®)
	d_i = 0.32 mm, d_f = 0.25 um
Pneumatics:	He; P_i = 10.0 psi;
	constant flow = 2.2 mL/min
Oven:	40°C (20 min), 10°C/min,
	240°C (20 min) for ZB-624
	50°C (20 min); 6°C/min;
	165°C (20 min) for ZB-WAXplus
Detector:	FID; 250° C

Standard preparation. USP Class 1 residual solvent mixture (#36279), USP residual solvents Class 2 - mixture A (#36271), and a USP residual solvents Class 2 - mixture B (#36280) were obtained from Restek. These standards were diluted in acccordance with the procedures outlined in USP <467>, Procedure A.

Sample preparation. A bottle of children's non-aspirin (acetaminophen) suspension liquid was purchased locally. The acetaminophen suspension was spiked to a level of 2000 µg/g with acetonitrile. Dilutions for headspace analysis were prepared in acccordance with the procedures outlined in USP <467>, Procedure A.

Headspace extraction. The samples were incubated in 10 mL headspace vials at 80°C for 60 minutes. One milliliter of sample headspace was introduced into the CIS 4 (140°C) in split mode with a split ratio of 2.5:1.

Results and Discussion

The GC analysis portion of USP <467> is divided into 3 procedures: A, B, and C. Procedures A and B are used to identify and provide semi-quantitative analysis results for any residual solvents. Procedure C is used for quantitation of residual solvents. Each procedure involves system suitability criteria followed by sample analysis. The method has been fully validated, therefore only a few criteria are required to proceed with sample analysis.

Procedure A

The system suitability requires running 3 solutions, the Class 1 system suitability, Class 1 standard, and the Class 2 mixture A standard solutions. The sample preparation steps for these solutions are described in the method [1]. The criteria which must be met are:

1. For the Class 1 system suitability solution, each peak must have a S/N ratio not less than three.
2. For the Class 1 standard solution, the 1,1,1-trichlorethane peak must have a S/N ratio of not less than five.
3. For the Class 2 mixture A standard solution, the resolution between the acetonitrile and methylene chloride peaks must not be less than one.

Figure 1 shows a chromatogram of the Class 1 system suitability solution on the Zebron™ ZB-624 column. The S/N ratio for the carbon tetrachloride peak is noted on the chromatogram. It is the smallest peak and has a S/N ratio greater than 3.

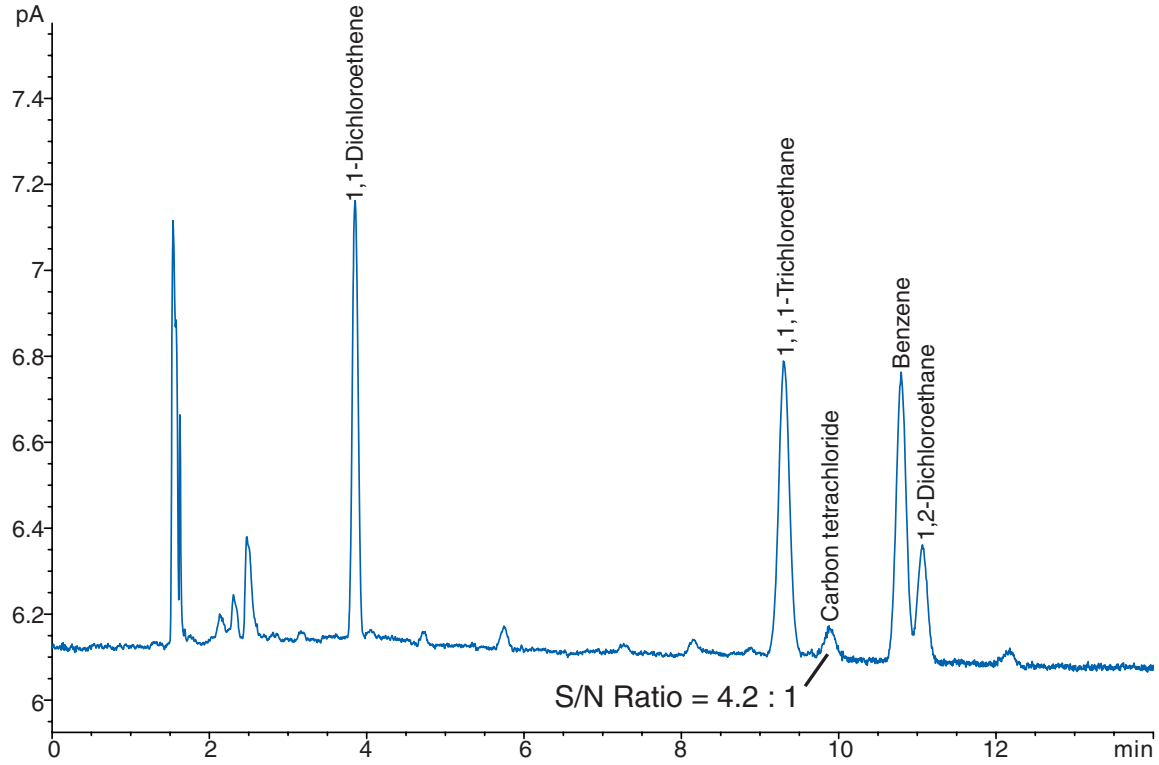

Figure 1. Chromatogram of the Class 1 system suitability solution on the Zebron™ ZB-624 column

Figure 2 shows a chromatogram of the Class 1 standard solution with the 1,1,1-trichlorethane peak having a S/N ratio of 14.

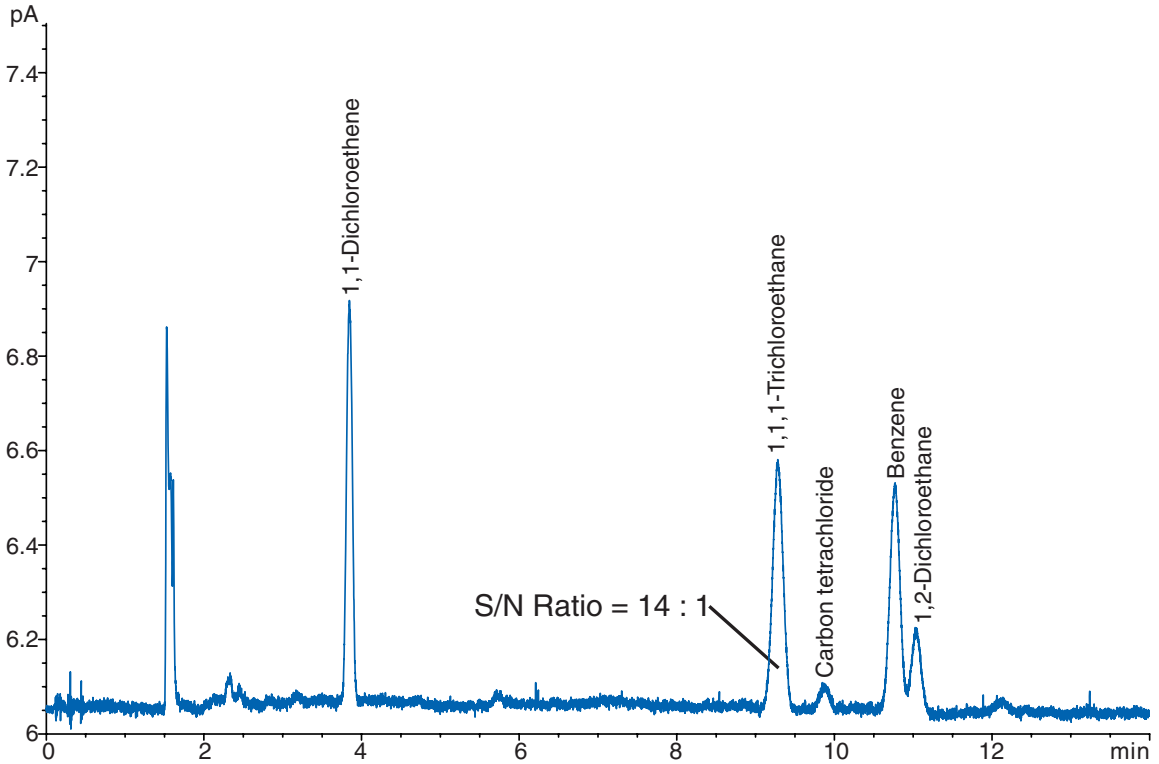

Figure 2. Chromatogram of the Class 1 standard solution on the Zebron™ ZB-624 column.

Figure 3 shows the Class 2 mixture A standard solution on the Zebron™ ZB-624 column with a resolution of 1.7 for the acetonitrile and methylene chloride peaks. The system passes the suitability criteria and the analysis can proceed with Procedure A.

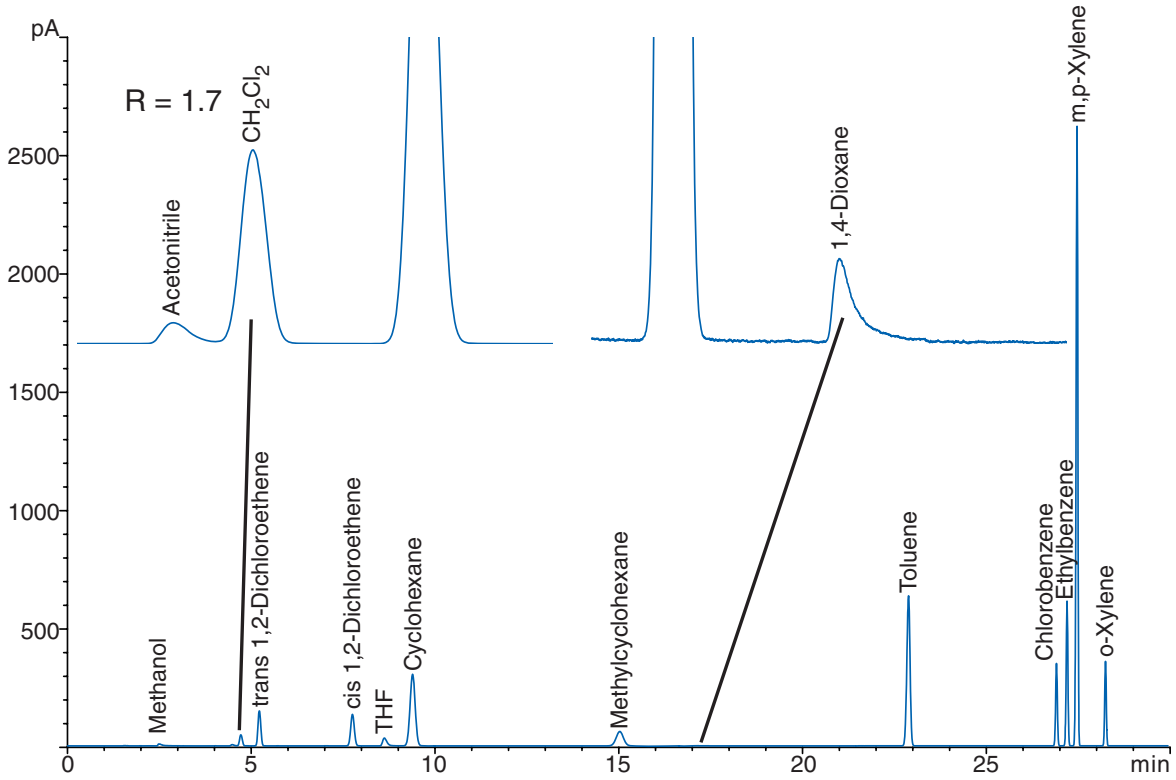

Figure 3. Chromatogram of the Class 2 mixture A standard solution on the Zebron™ ZB-624 column.

For Procedure A, the Class 1 standard solution, Class 2 mixture A and mixture B standard solutions and the test solution are run under the same headspace and chromatographic conditions used for the system suitability procedure. Any peak in the test solution which has a peak area greater than or equal to a corresponding peak in any of the standard chromatograms is verified using Procedure B.

Figure 4 shows a chromatogram for the Class 2 mixture B standard solution.

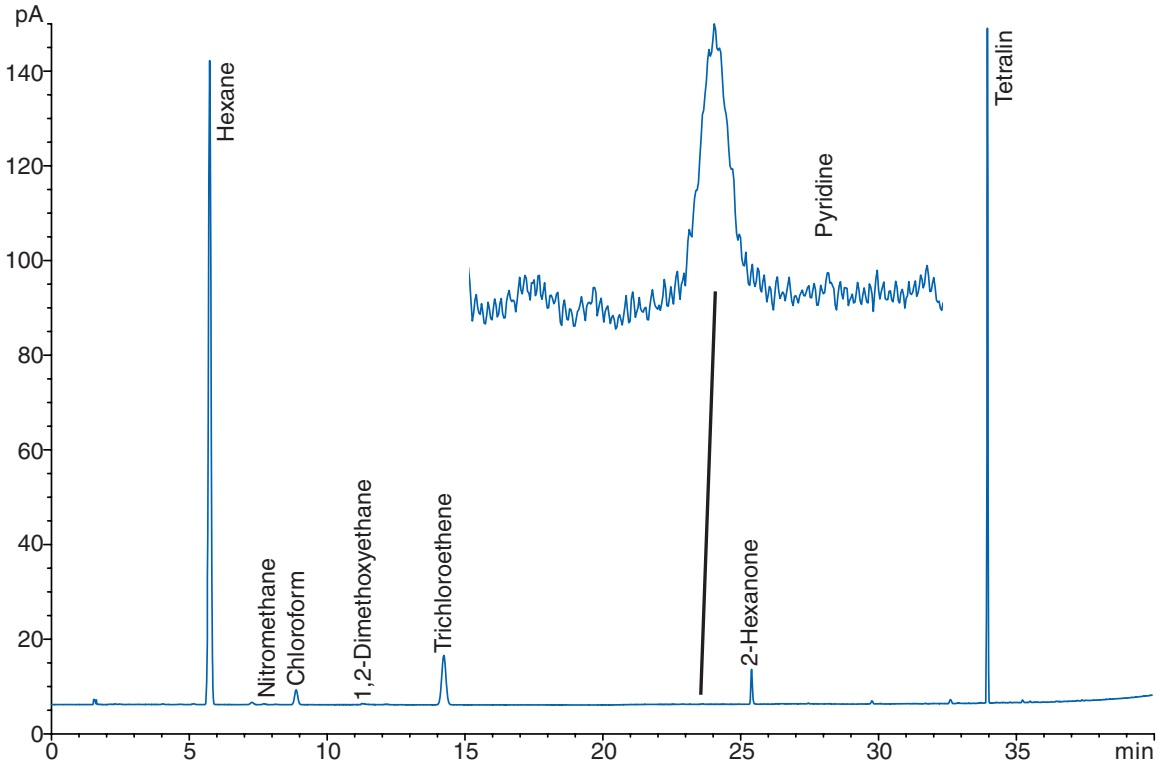

Figure 4. Chromatogram for the Class 2 mixture B standard solution on the Zebron™ ZB-624 column.

Figure 5 shows an overlay of the Class 2 mixture A standard solution and test solution. In this example, the acetonitrile peak is greater than that in the Class 2 mixture A standard solution chromatogram, which means it must be verified using Procedure B. Though not required by the method, multiple injections (n=3) were made for the Class 1, Class 2 mixture A and Class 2 mixture B standard solutions. The results are listed in Tables 1-3, respectively. The range for the precision is 0.65-15.7%, with an average value of 4.7%.

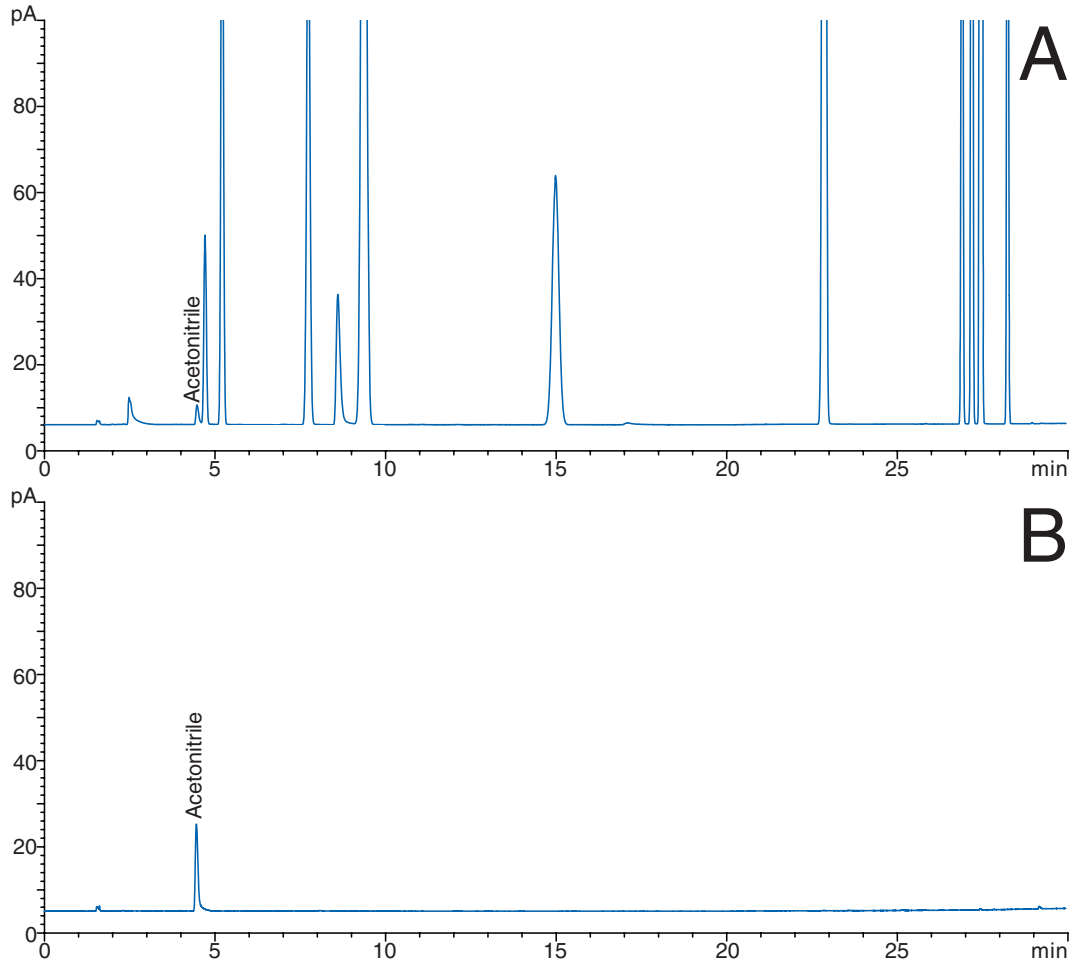

Figure 5. Stacked view of the Class 2 mixture A standard solution (A) and test solution (B).

These results demonstrate that the MPS 2 autosampler, when configured to perform the headspace method described in USP <467>, meets the required suitability criteria for the method.

Table 1. Precision data (n=3) Class 1 standard solution.

Compound	%RSD
Benzene	2.61
CCl_4	3.34
1,2-Dichloroethane	5.15
1,1-Dichloroethene	0.69
1,1,1-Trichloroethane	0.65

Table 2. Precision data (n=3) Class 2 mixture A standard solution.

Compound	%RSD
Methanol	6.02
Acetonitrile	15.7
CH_2Cl_2	3.81
trans-1,2-Dichloroethene	2.62
cis-1,2-Dichloroethene	3.17
THF	6.26
Cyclohexane	6.37
Methylcyclohexane	6.23
1,4-Dioxane	13.6
Toluene	2.67
Chlorobenzene	3.52
Ethylbenzene	2.86
m,p-Xylene	2.90
o-Xylene	3.14

Table 3. Precision data (n=3) Class 2 mixture B standard solution.

Compound	%RSD
Hexane	2.87
Nitromethane	10.8
Chloroform	2.37
1,2-Dimethoxyethane	3.61
Trichloroethene	1.23
Pyridine	6.47
2-Hexanone	4.27
Tetralin	3.03

Procedure B

For Procedure B, the system suitability test requires running 3 solutions: The Class 1 system suitability solution, Class 1 standard, and the Class 2 mixture A standard solutions on a wax phase column. A 30 m x 0.32 mm x 0.25 µm Zebron™ ZB-WAXplus was installed for this part of the study. The sample preparation steps for these solutions are described in the method [1]. The criteria which must be met for Procedure B are:

1. For the Class 1 system suitability solution, each peak must have a S/N ratio not less than three.
2. For the Class 1 standard solution, the benzene peak must have a S/N ratio of not less than five.
3. For the Class 2 mixture A standard, the resolution between the acetonitrile and cis-dichloroethene peaks must not be less than one.

The Class 1 standard solution, Class 2 mixture A and mixture B standard solutions and the test solution are run under the same headspace and chromatographic conditions as the system suitability solution.

Figure 6 shows a chromatogram of the Class 1 system suitability solution run on the WAXplus phase column. The smallest peak is 1,2-dichloroethane with a S/N ratio of 28 which means that the first criterion is met.

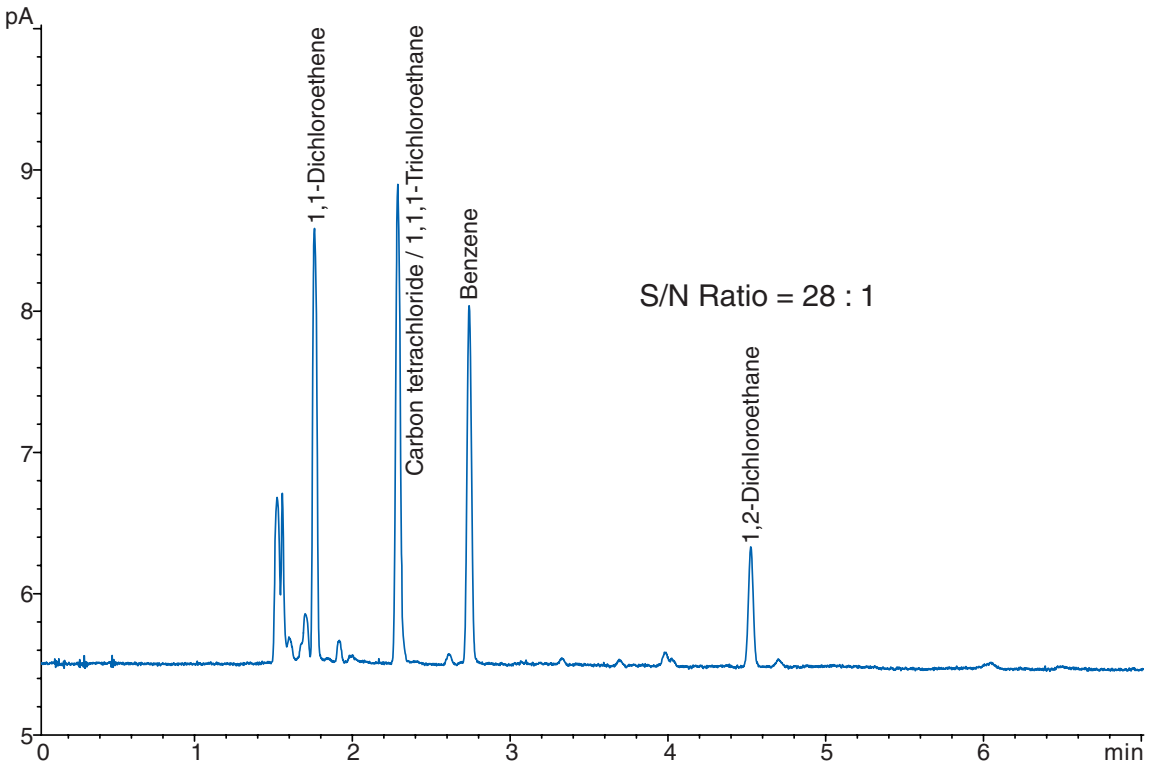

Figure 6. Chromatogram of the Class 1 system suitability solution on the Zebron™ ZB-WAXplus.

Figure 7 shows a chromatogram of the Class 1 standard solution on the wax column. The S/N ratio for benzene is 90, which means that the second criterion is met.

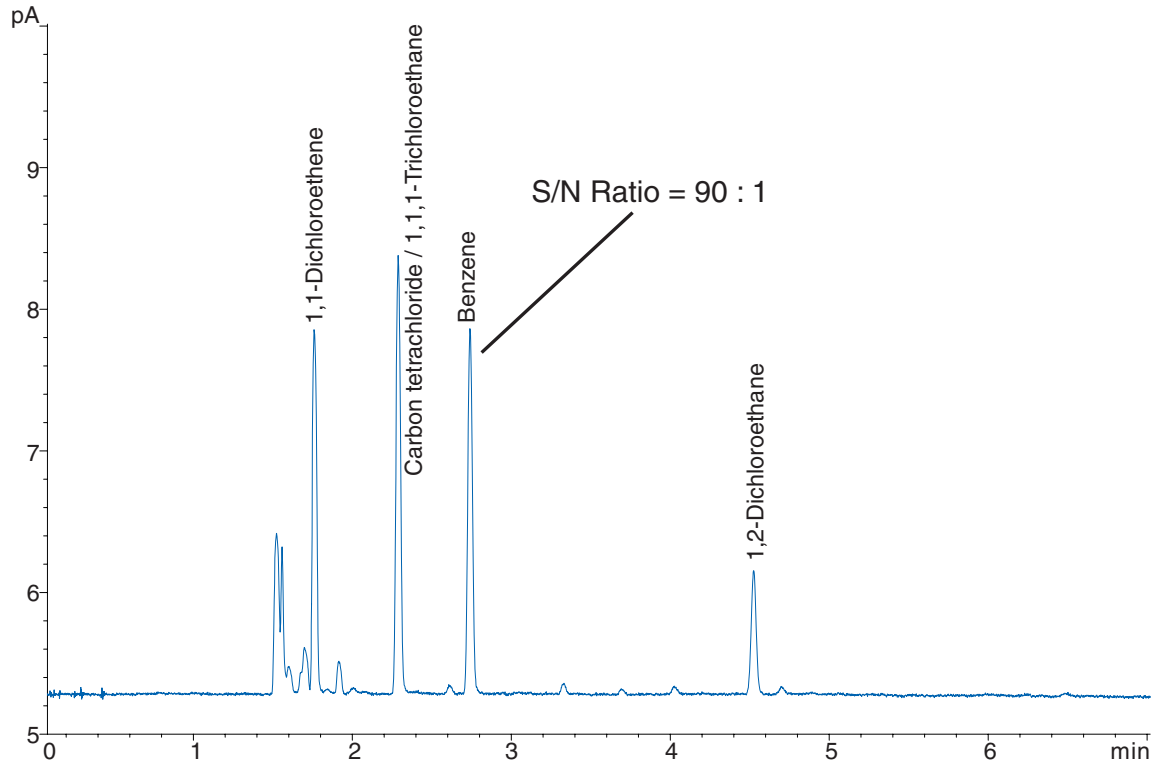

Figure 7. Chromatogram of the Class 1 standard solution on the Zebron™ ZB-WAXplus.

Figure 8 shows a chromatogram of the Class 2 mixture A standard solution run on the wax column. The resolution of the acetonitrile and cis-dichloroethene peaks is 2.7, which means that the final criterion for Procedure B is met.

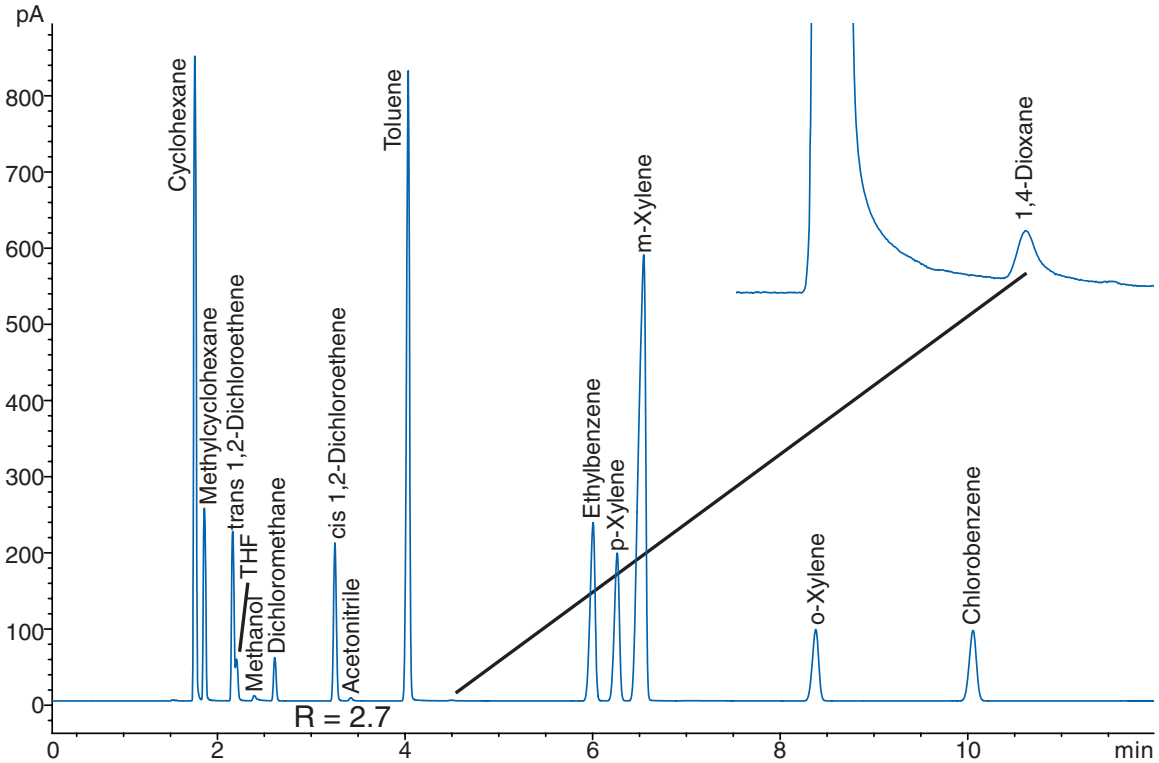

Figure 8. Chromatogram of the Class 2 mixture A standard solution on the Zebron™ ZB-WAXplus.

The test solution can now be run and the peak heights of any analytes found compared to that of the standards solutions. Figure 9 shows the Class 2 mixture B standard solution run on the wax column.

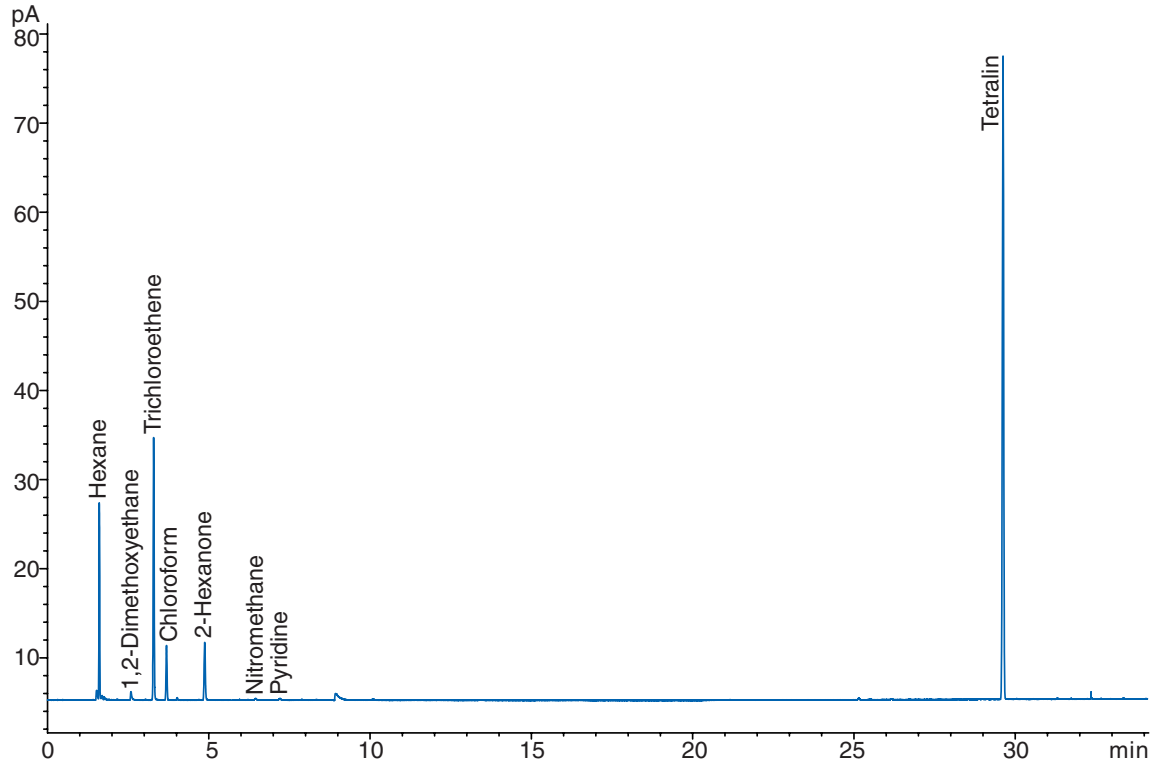

Figure 9. Chromatogram for the Class 2 mixture B standard solution on the Zebron™ ZB-WAXplus.

Figure 10 shows an overlay of the test solution and the Class 2 mixture A standard solution chromatograms. The acetonitrile peak is confirmed and its height is greater than that found in the Class 2 mixture A standard. Therefore, it must be quantitated using Procedure C.

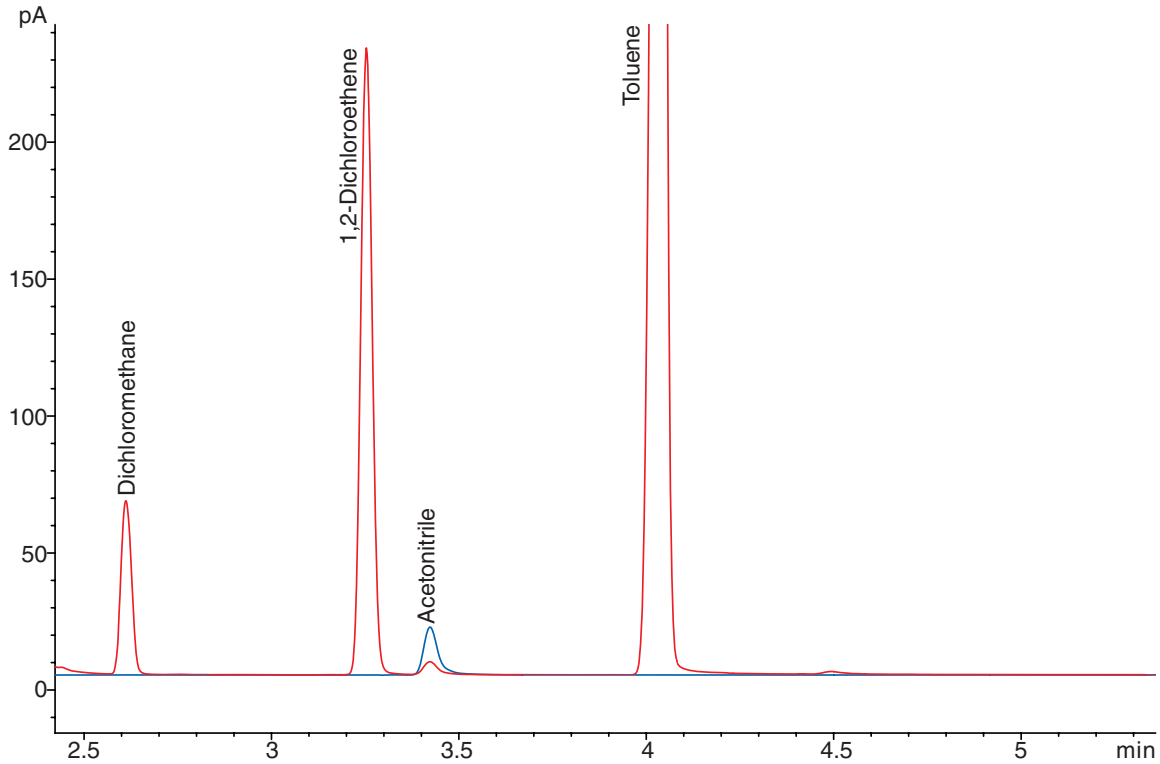

Figure 10. Overlay of the Class 2 mixture A standard solution (red) and test solution (blue).

Though not required by the method, multiple injections (n=3) were made for the Class 1, Class 2 mixture A and Class 2 mixture B standard solutions. The results are listed in tables 4-6, respectively. The range for the precision is 0.79-9.43%, with an average value of 4.8%.

Table 4. Precision data (n=3) Class 1 standard solution.

Compound	%RSD
1,1-Dichloroethene	5.00
1,1,1-Trichloroethane/CCl4	5.36
Benzene	1.63
1,2-Dichloroethane	3.98

Table 5. Precision data (n=3) Class 2 mixture A standard solution.

Compound	%RSD
Cyclohexane	1.49
Methylcyclohexane	1.59
trans-1,2-Dichloroethene	4.79
Tetrahydrofuran	7.63
Methanol	6.13
Dichloromethane	6.40
cis-1,2-Dichloroethene	5.67
Acetonitrile	9.43
Toluene	5.00
1,4-Dioxane	4.70
Ethyl Benzene	4.88
p-Xylene	8.38
m-Xylene	5.03
o-Xylene	5.53
Chlorobenzene	5.93

Table 6. Precision data (n=3) Class 2 mixture B standard solution.

Compound	%RSD
Hexane	0.79
1,2-Dimethoxyethane	9.28
Trichloroethene	1.76
Chloroform	2.39
2-Hexanone	5.25
Nitromethane	3.89
Pyridine	5.27
Tetralin	1.38

Procedure C

For Procedure C, the 30 m x 0.32 mm x 1.8 µm Zebron™ ZB-624 column was used. The system suitability criteria are the same as for Procedure A and system suitability testing was therefore not repeated for Procedure C. The spiked test solution and test solution are run when the system suitability criteria are met. The spiked test solution was prepared as described in the method [1].

The concentration of residual solvent in the article is calculated using the following equation:

$$\text{concentration (ppm)} = 5(C/W)[r_u/(r_{st}-r_u)]$$

where C is the concentration, in µg/mL, of the reference standard in the standard solution; W is the weight, in g, of the sample of the article under test taken to prepare the test stock solution; and r_u and r_{st} are the peak responses of each residual solvent obtained from the test solution and the spiked test solution, respectively. [1] The results for (n=3) replicates of the test solution gave an average value of 1770 ppm, with an RSD of 2.0%.

Though not required by the method, a calibration curve was made for acetonitrile. Figure 11 shows a seven point calibration curve for acetonitrile over the range 0-500 ppm. The linear regression shows excellent linearity with an r^2 value of 0.9998.

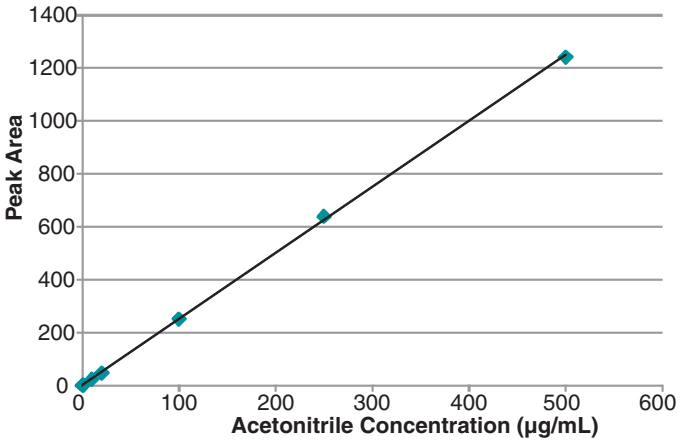

Figure 11. Calibration curve for acetonitrile.

Conclusions

Recent guidance from the USP [2] gives parameters for using syringe based autosamplers for USP <467>. This study demonstrates that acceptable precision, linearity and accuracy can be achieved using the GERSTEL MPS 2 for determination of residual solvents following USP <467>.

GERSTEL MAESTRO software in PrepAhead mode was used to control the MPS 2 autosampler. In PrepAhead mode, samples are incubated while the preceding sample is being analyzed ensuring that the GC doesn't have to wait idly for the next injection and thereby providing best possible productivity and throughput. However the MPS 2 autosampler can also be operated directly from the handheld keypad to perform this headspace method. The MPS 2 autosampler can also be easily configured to run liquid injection, large volume liquid injection, Dynamic Headspace, Solid Phase Microextraction (SPME) or perform sample preparation as the needs of the laboratory change.

References

[1] <467> Residual Solvents, The United States Pharmacopeia Convention, Rockville, Maryland, USA, 2007.

[2] USP 32 NF27, General Chapter <467> Residual Solvents, Table 5, The United States Pharmacopeial Convention, Rockville, Maryland, USA, 2008.

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