USP 467
ANALYSIS OF RESIDUAL SOLVENTS

Technology Advantage: Agilent Intuvo 9000 GC with HS

Introduction

Analysis of residual solvent is a critical application in the pharmaceutical industry. The choice of solvent during manufacturing can improve yield or typically affect the chemical properties of the product synthesized. However, solvents do not enhance the product's efficacy, and must be removed as completely as possible to meet product specifications and good manufacturing practices[1]. Therefore, testing for residual solvents during production or purification processes is a necessary aspect of manufacturing.

Analysis of residual solvents according to USP 467 was evaluated on an Agilent Intuvo system equipped with a headspace sampler. The Agilent Intuvo 9000 Gas Chromatograph yields advantages over conventional GC systems:

- Modular flow path for simplified sample splitting to two columns
- Quick column changes for easier method development
- Smaller footprint

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Experimental

An Intuvo 9000 GC was equipped with an Agilent 7697A Headspace Sampler. Class 1, Class 2a, and Class 2b standard solutions were prepared and evaluated according to USP 467 methodology.

Instrument conditions.

Parameter	Value
Agilent Intuvo 9000 GC	
Inlet	140 °C Split 5:1
Column	Agilent J&W DB-Select 624 Ultra Inert Intuvo, 30 m × 0.32 mm, 1.8 µm (p/n 123-0334UI-INT)
Column flow	2 mL/min
Oven	40 °C (5 minutes) then 15 °C/min to 180 °C (3 minutes)
Jumper chip	250 °C
FID	250 °C
Agilent 7697A Headspace Sampler	
Oven	85 °C
Loop	85 °C
Transfer line	100 °C
Vial equilibration	40 minutes
Injection duration	0.5 minutes
Vial	10 mL
Shaking	On, level 2
Vial fill flow	50 mL/min
Vial fill pressure	15 psi
Vial pressure equilibration time	0.05 minutes
Loop fill ramp rate	20 psi/min
Final loop pressure	10 psi
Loop equilibration	0.05 minutes

Results and Discussion

Eight headspace vials were prepared for each solvent standard (Classes 1, 2a, and 2b), and repeatability was evaluated. Repeatability was very good, with all but one compound yielding RSDs of less than 5 % (Tables 1–3). While USP 467 does not have specific RSD requirements, 5 % RSD is an acceptable level for most laboratories.

Figures 1–3 show chromatograms for the three solvent classes. Tables 1–3 also list the corresponding analyte number.

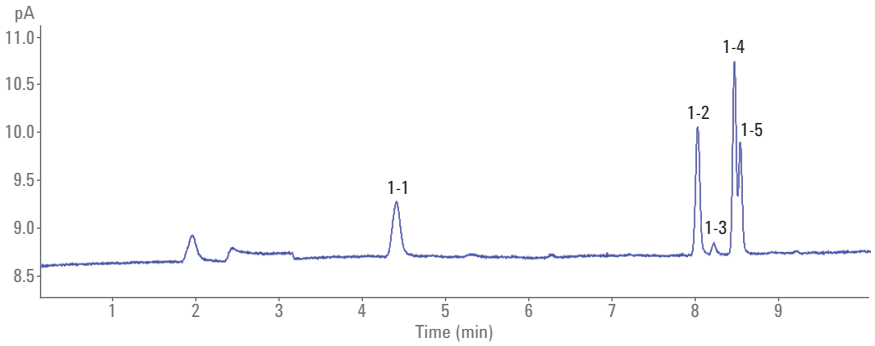

Figure 1. Class 1 standard chromatogram.

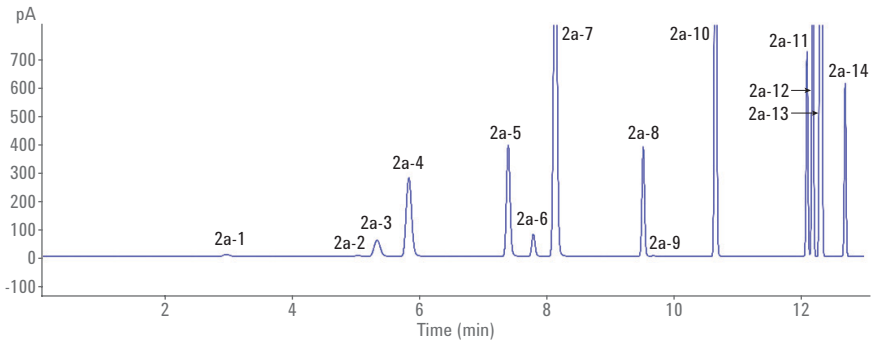

Figure 2. Class 2a standard chromatogram.

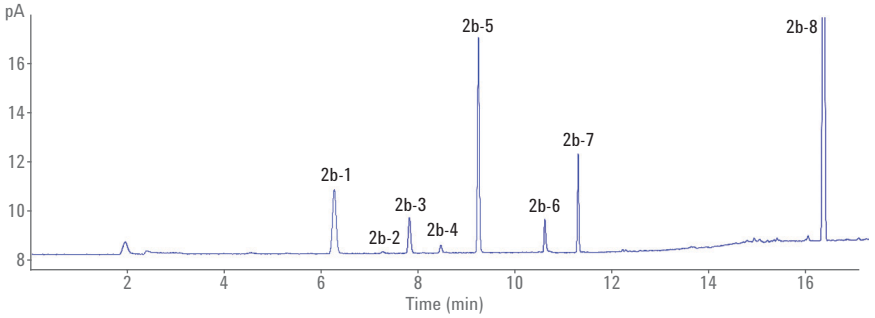

Figure 3. Class 2b standard chromatogram.

Table 1. Class 1 solvent standard repeatability.

Class 1	RSD %
1,1-Dichloroethane (1-1)	2.7
1,1,1-Trichloroethane (1-2)	2.1
Carbon tetrachloride (1-3)	4.5
Benzene (1-4)	1.9
1,2-Dichlorobenzene (1-5)	0.93
1,1-Dichloroethane (1-6)	2.7

Table 2. Class 2a solvent standard repeatability.

Class 2a	RSD %
Methanol	1.3
Acetonitrile	0.98
Dichloromethane	1.3
***trans*-1,2-Dichloroethene**	2.4
***cis*-1,2-Dichloroethene**	1.7
Tetrahydrofuran	0.69
Cyclohexane	2.5
Methylcyclohexane	2.7
1,4-Dioxane	1.1
Toluene	2.1
Chlorobenzene	1.8
Ethylbenzene	2.3
***m,p*-Xylene**	2.3
***o*-Xylene**	2.1

Table 3. Class 2b solvent standard repeatability.

Class 2b	RSD%
Hexane	4.6
Nitromethane	6.7
Chloroform	4.2
1,2-Dimethoxyethane	3.7
Trichloroethylene	4.6
Pyridine	2.8
2-Hexanone	2.9
Tetralin	3.6

The three standard solutions were then mixed to evaluate the three classes in a single run. Figure 4 shows the resulting chromatogram. The differences in concentration and coelutions of multiple compounds demonstrate the need to run these as separate mixes, or use additional analytical techniques.

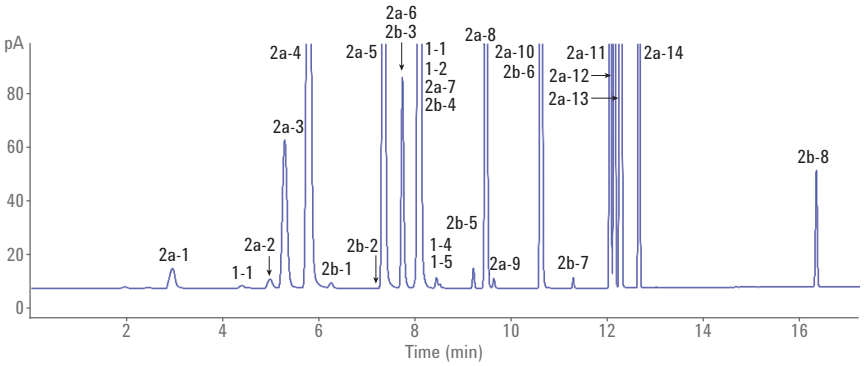

Figure 4. USP 467 Class 1, 2a, and 2b in a single headspace vial.

Conclusion

The Agilent Intuvo 9000 GC equipped with the Agilent 7697A Headspace Sampler delivers excellent repeatability performance for USP 467 class 1, 2a, and 2b solvent standards*. However, when attempting to analyze the three mixes together, difficulties arise due to differences in concentration and coeluting analytes. Additional analytical techniques such as splitting to two columns for dual detector analysis or using a mass spectrometer as a detector would improve detection and identification of the analytes in a single mix, and will be discussed in a separate Application Brief.

* For a majority of the analytes evaluated, RSD was less than 3 %.

Reference

1. www.usp.org/sites/default/files/usp-pdf/EN/USPNF/generalChapter467Current.pdf

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Information, descriptions and specifications in this publication are subject to change without notice.

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