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Application News

Residual Solvents Analysis in Pharmaceuticals by HS-GC-FID with Newly Added Compounds – USP <467> Procedure A

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User Benefits

- Good separation was achieved with newly added compounds
- Cost effective when using nitrogen as carrier gas instead of helium

■ Introduction

United States Pharmacopeia (USP) <467> Residual Solvents is a compendium that defines acceptable amounts of residual solvents in pharmaceuticals and provides procedures to analyze residual solvents [1]. The recommended limit or classification of the solvent in USP <467> would be updated when new safety data on more solvents become available [2]. Methyl isobutyl ketone was reclassified as a Class 2 solvent in USP <467> in 2020 (previously a Class 3 solvent). Meanwhile, tertiary butyl alcohol and cyclopentyl methyl ether were proposed to be classified as Class 2 residual solvents in 2021 [1][2]. Here, we describe headspace-gas chromatography (HS-GC) method using nitrogen carrier gas to analyse Class 1 and Class 2 solvents, following USP<467> Procedure A, updated with 3 new solvents, namely cyclopentyl methyl ether, tertiary butyl alcohol and methyl isobutyl ketone.

■ Measurement Conditions and Samples

HS-20 NX headspace autosampler paired with Nexis GC-2030 (Shimadzu Corporation, Japan) were used in this work. The analytical conditions following Procedure A under water-soluble article section in USP<467> are shown in Table 1.

Certified USP<467> Class 1 and 2 mixed standard solutions (without cyclopentyl methyl ether, tertiary butyl alcohol and methyl isobutyl ketone) were purchased from Restek Corporation, USA. The standards were prepared according to USP<467> Procedure A. Cyclopentyl methyl ether, tertiary butyl alcohol and methyl isobutyl ketone were purchased from Tokyo Chemical Industry (TCI). A mixture containing these 3 compounds was prepared in dimethyl sulfoxide at these concentrations: 7,500 µg/ml (cyclopentyl methyl ether), 17,500 µg/ml (tertiary butyl alcohol) and 22,500 µg/ml (methyl isobutyl ketone). Then, this mixture and Class 2A standard solution were mixed and further diluted following USP <467> Procedure.

Table 1: HS-GC analytical conditions for residual solvent analysis following USP <467>

Instruments and Column information	
GC-FID	Nexis GC-2030
Auto Injector	HS-20 NX
Column	SH-I-624Sil MS 30 m x 0.32 mm ID x 1.80 µm df
Detector	FID-2030 Flame Ionization Detector
HS parameter	
Oven Temperature	80 °C
Sample Line Temperature	110 °C
Transfer Line Temperature	120 °C
Injection Time	1 min
Pressurizing Gas Pressure	75 kPa
Equilibrating Time	60 min
Shaking Level	2
GC-FID parameter	
Injection Mode	Split mode Split ratio 5
Carrier Gas	Nitrogen
Gas Flow Condition	Constant linear velocity mode Linear velocity 35 cm/s
Oven Temperature Programming	40 °C (20 min) →10 °C/min to 240 °C (20 min)
Detector Temperature	250 °C
Hydrogen Flow	32 mL/min
Synthetic Air Flow	200 mL/min
Make-up Gas Flow	24 mL/min

Table 2: Peak area repeatability and average signal to noise ratio (S/N) for Class 1 Standard

Peak No.	Solvent	%RSD of peak area (n=7)	Average S/N ratio (n=7)
1	1,1-Dichloroethene	4.6	118
2	1,1,1-Trichloroethane	3.6	114
3	Carbon tetrachloride	5.3	8
4	Benzene	4.0	146
5	1,2-Dichloroethane	4.1	56

■ Results

Class 1 Standard

Class 1 result is displayed in Table 2. The average S/N value (n=7) for 1,1,1-trichloroethane (peak 2) is 114, which is much greater than the requirement stated in USP<467> (i.e., S/N ratio is not less than 5). Carbon tetrachloride (peak 3), which sensitivity is the lowest among the Class 1 solvents, has an average S/N value of 8. The repeatability of peak areas, %RSD (n=7) obtained from the 5 solvents ranges from 3.6% to 5.3%. These results indicate that this HS-GC method using nitrogen carrier gas can achieve the sensitivity requirement as stated in the USP<467> Procedure A for Class 1 Standards.

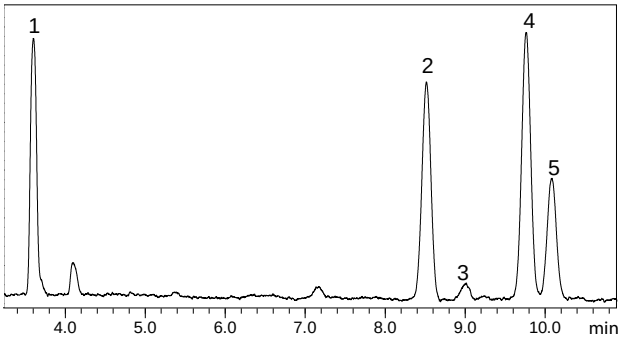

Figure 1: HS-GC-FID chromatogram of Class 1 Standard following Procedure A in USP<467>. Peak labelling refers to Table 2.

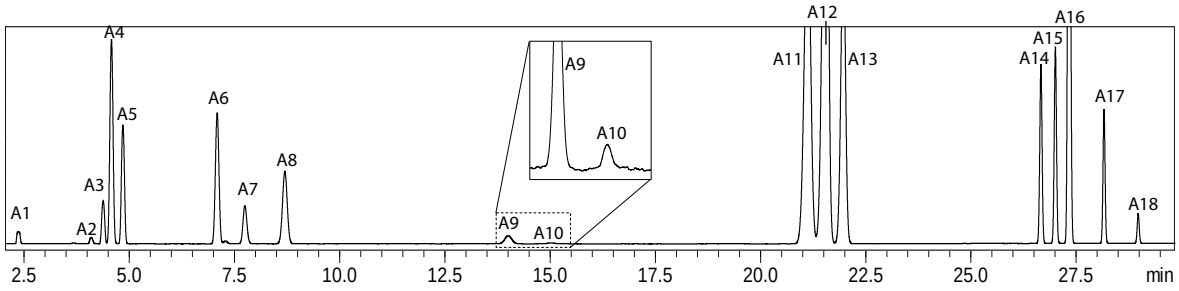

Figure 2: Chromatogram of Class 2A Standard analysed using Procedure A. Refer to Table 3 for the peak labeling.

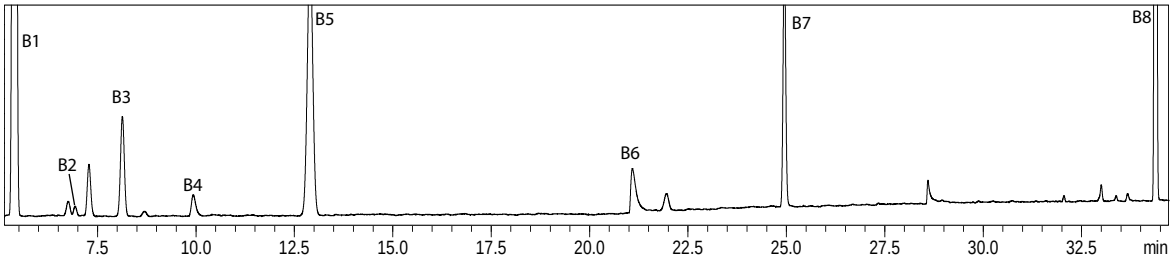

Figure 3: Chromatogram of Class 2B Standard analysed using Procedure A. Refer to Table 3 for the peak labeling.

Class 2 Standard

Class 2 Standard consists of two groups, Class 2A and Class 2B. The chromatograms are shown in Figure 2 and 3, respectively. The repeatability results of Class 2A and Class 2B are compiled into Table 3. The peak area %RSD (n=7) values obtained for all the solvents ranges from 0.6% to 6.7%.

Acetonitrile and methylene chloride were well separated as shown in Figure 2. The specific resolution (R_s) between acetonitrile and methylene chloride obtained was 2.2. This meets the stated criteria of USP<467> that R_s of these 2 compounds must not be less than 1. Even with three new compounds added into Class 2A standard mixture, all the peaks were well separated (Figure 2).

■ Conclusion

HS-20 NX with Nexis GC-2030 with nitrogen carrier gas successfully achieved the required sensitivity (S/N) and peak resolution stated in the criteria of USP<467> Procedure A. Good separation of Class 2A solvents was maintained even with the addition of three new compounds, namely cyclopentyl methyl ether, tertiary butyl alcohol and methyl isobutyl ketone.

■ References

1. The United States Pharmacopeia, USP <467> RESIDUAL SOLVENTS.
2. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 2021, *IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C(R8)*, accessed 15 December 2021 <https://database.ich.org/sites/default/files/ICH_Q3C-R8_Guideline_Step4_2021_0422_1.pdf>

Table 3: Peak area repeatability (n=7) for Class 2A and 2B Standards

Class 2A standard		
No.	Compound	%RSD (n=7) of peak area
A1	Methanol	0.6
A2	Acetonitrile	0.7
A3	Methylene chloride	3.2
A4	Tertiary Butyl Alcohol	0.6
A5	trans-1,2-Dichloroethylene	3.8
A6	Cis-1,2-Dichloroethylene	3.3
A7	Tetrahydrofuran	0.7
A8	Cyclohexane	3.8
A9	Methylcyclohexane	4.0
A10	1,4-Dioxane	6.7
A11	Cyclopentyl Methyl Ether	1.7
A12	Methylisobutyl Ketone	1.2
A13	Toluene	3.2
A14	Chlorobenzene	3.1
A15	EthylBenzene	3.2
A16	m,p-Xylene	3.1
A17	o-xylene	3.0
A18	Cumene	3.2
Class 2B standard		
No.	Compound	%RSD (n=7) of peak area
B1	Hexane	6.7
B2	Nitromethane	5.3
B3	chloroform	3.9
B4	1,2-dimethoxyethane	4.9
B5	trichloroethylene	5.3
B6	Pyridine	3.8
B7	2-hexanone	1.0
B8	Tetralin	3.6

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