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Application News

No. G326A

Gas Chromatography

Analysis of Residual Solvents in Pharmaceuticals by Water-Insoluble Samples Using N_2 Carrier (JP18, USP 467)

The Japanese Pharmacopoeia 18th Edition (JP18) and the United States Pharmacopeia (USP) General Chapter <467> Residual Solvents provide test methods for residual solvents in pharmaceuticals, mainly using headspace gas chromatography (GC). Residual solvents in pharmaceuticals are classified from Class 1 to 3 based on their potential human health risk. Since these compounds are strictly controlled, highly sensitive analysis is required. Helium (He) is generally used as the carrier gas, but as He supply shortages have become an issue recently, analysis using an alternative carrier gas such as N_2 has also been in demand lately. Any method changes, such as substituting He with an alternate carrier gas, must be validated according to USP General Chapter <1467> Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures.

This article introduces a JP18- compliant analysis of water-insoluble samples for Class 1 and 2 residual solvents using N_2 as the carrier gas.

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Instrument Configuration and Analysis Conditions

Class 1 and 2 standard solutions were prepared and measured in accordance with Procedure A and B of JP18, using Shimadzu HS-20 headspace gas sampler connected to Nexis™ GC-2030 gas chromatograph. The two procedures differ in the type of column, the column temperature and the split ratio. Table 1 lists the GC and HS-20 analysis conditions used in this experiment.

Table 1 **Water-Insoluble Sample Analysis Conditions**

GC analysis conditions (Procedure A and B)	
Model	: Nexis GC-2030
Detector	: FID-2030 flame ionization detector
Column	: A) SH-Rxi™-624 Sil MS (0.53 mm I.D. × 30 m, d.f.= 3 µm) B) SH-Stabilwax™ (0.32 mm I.D. × 30 m, d.f.= 0.25 µm)
Column temp.	: A) 40 °C (20 min) - 10 °C /min - 240 °C (20 min) Total 60 mins B) 50 °C (20 min) - 6 °C /min - 165 °C (20 min) Total 59.17 mins
Injection mode	: A) Split 1:5 B) Split 1:10
Carrier gas controller	: Linear velocity (N_2)
Linear velocity	: 35 cm/sec
Detector temp.	: 250 °C
FID H_2 flow rate	: 32 mL/min
FID make up flow rate	: 24 mL/min (N_2)
FID air flow rate	: 200 mL/min
Injection volume	: 1 mL
HS-20 analysis conditions (same for Procedure A and B)	
Oven temp.	: 80 °C
Sample line temp.	: 90 °C
Transfer line temp.	: 105 °C
Vial shaking level	: Off
Vial volume	: 20 mL
Vial equilibrating time	: 45 min
Vial pressurizing time	: 1 min
Vial pressure	: 68.9 kPa
Loading time	: 0.5 min
Needle flush time	: 5 min

Analysis of Class 1 Standard Solution (Water-Insoluble Sample)

Fig. 1 and 2 show the analysis results for Procedure A and B respectively. Table 2 and 3 show the S/N ratios and the repeatability of the two procedures respectively.

Satisfactory results were obtained with Procedure A, meeting the requirements of JP18 which states that "the S/N ratio for 1,1,1-trichloroethane in the Class 1 standard

solution is not less than 5 and the relative standard deviation of each peak area is not more than 15 %." Results obtained with Procedure B were also satisfactory as "the S/N ratio for benzene in the Class 1 standard solution is not less than 5 and the relative standard deviation of each peak area is not more than 15 %."

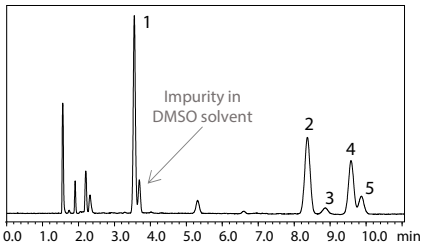

Fig. 1 **Chromatogram of Class 1 Standard Solution by Procedure A (Water-Insoluble Sample)**

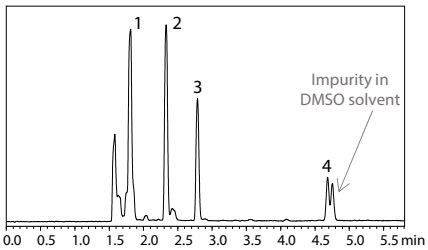

Fig. 2 **Chromatogram of Class 1 Standard Solution by Procedure B (Water-Insoluble Sample)**

Table 2 **S/N Ratio and Repeatability of Class 1 Standard Solution (Procedure A)**

Peak No.	Compound	S/N ratio*1	%RSD (n=6)*1
1	1,1-Dichloroethane	325	2.95
2	1,1,1-Trichloroethane	140	3.08
3	Carbon tetrachloride	12	2.83
4	Benzene	140	2.72
5	1,2-Dichloroethane	46	1.67

Table 3 **S/N Ratio and Repeatability of Class 1 Standard Solution (Procedure B)**

Peak No.	Compound	S/N ratio*1	%RSD (n=6)*1
1	1,1-Dichloroethane	290	2.15
2	1,1,1-Trichloroethane +Carbon tetrachloride	383	3.44
3	Benzene	188	3.79
4	1,2-Dichloroethane	94	1.46

In Table 2 and 3, the items specified in JP18 are shown in red.

*1 The S/N ratios and relative standard deviation (%RSD) are reference values and not intended to be guaranteed values.

Analysis of Class 2 Standard Solution (Water-Insoluble Sample)

Fig. 3 and 4 show the analysis results for Procedure A and B (Black: Class 2 mixture A standard solution (Class 2A), Pink: Class 2 mixture B standard solution (Class 2B), Blue: MIBK).

For system suitability, JP18 specifies that "the resolution between acetonitrile and methylene chloride in the Class 2 mixture A standard solution is not less than 1.0" when using Procedure A and "the resolution between acetonitrile and *cis*-1,2-dichloroethene in the Class 2 mixture A standard solution is not less than 1.0" when using Procedure B. Satisfactory results were obtained with both procedures.

* The resolutions shown in the Fig. 3 and 4 are reference values and not guaranteed.

Conclusion

Using a N_2 carrier gas, the analysis achieved the accuracy levels required by Japanese Pharmacopoeia 18th Edition and USP General Chapters <467> and <1467>. In the analysis of residual solvents in water-insoluble pharmaceuticals using the headspace GC method, the results obtained with N_2 as the carrier gas were satisfactory and comparable to those with He as the carrier gas.

For information about using a H_2 carrier for analysis of residual solvents in pharmaceuticals using water-insoluble samples, refer to Application News 01-00177-EN.

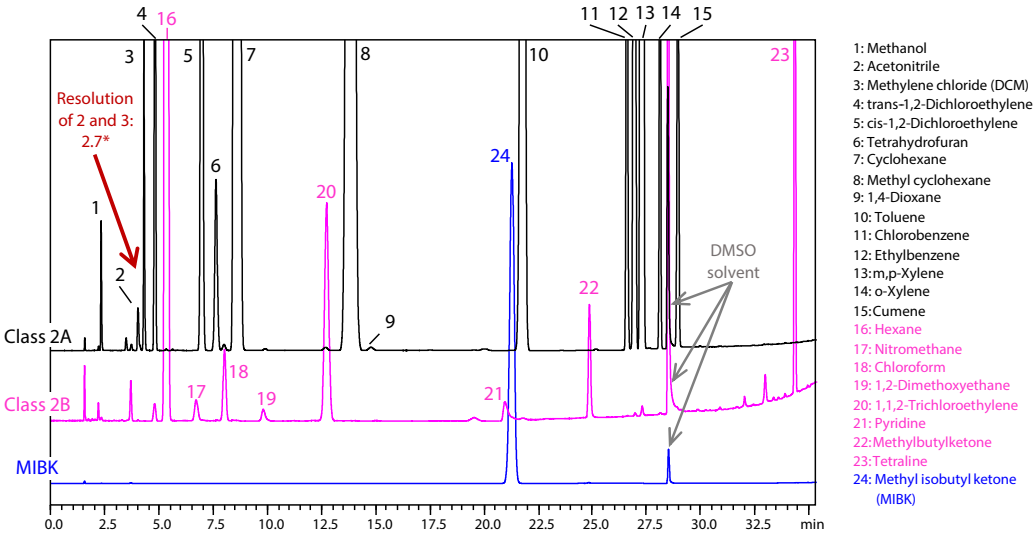

Fig. 3 **Chromatogram of Class 2 Standard Solution by Procedure A (Water-Insoluble Sample)**

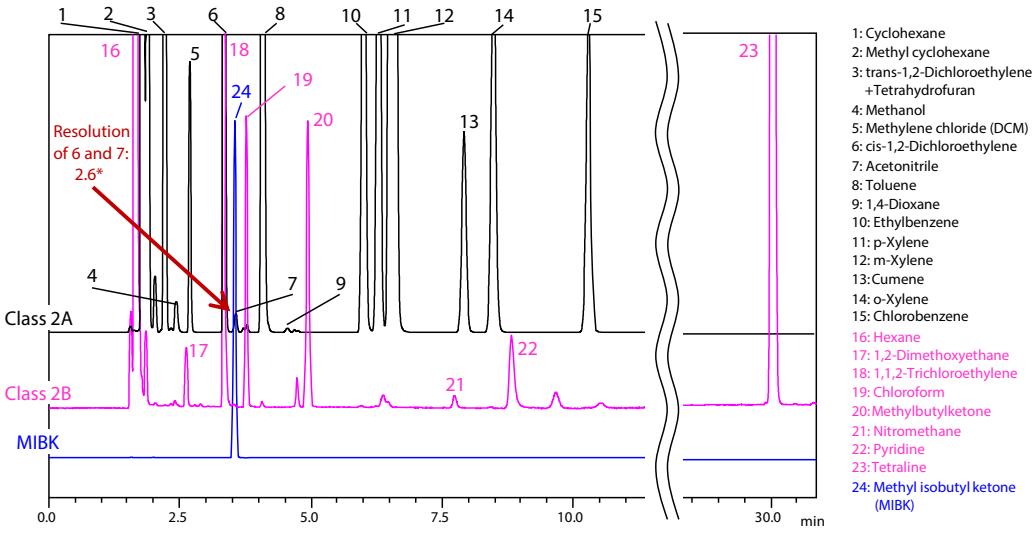

Fig. 4 **Chromatogram of Class 2 Standard Solution by Procedure B (Water-Insoluble Sample)**

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