Application News

No. G326

Gas Chromatography

Analysis of Residual Solvents in Pharmaceuticals by Water-Insoluble Samples Using N₂ Carrier (JP17 Supplement II, USP 467)

The Japanese Pharmacopoeia 17th Edition (JP17) and the United States Pharmacopeia (USP) General Chapters <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 analysis using an alternative carrier gas such as N_2 has also been in demand recently as He supply shortages have become an issue in recent years.

This article introduces a JP17 Supplement II- compliant analysis of water-insoluble samples for Class 1 and 2 residual solvents using N_2 as the carrier gas.

N. Iwasa, T. Wada

■ Instrument Configuration and Analysis Conditions

Class 1 and 2 standard solutions were prepared and measured in accordance with Procedure A and B of JP17 Supplement II, 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 stirring	: Off
Vial volume	: 20 mL
Vial heat-retention time	: 45 min
Vial pressurization 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 JP17 Supplement II 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 %."
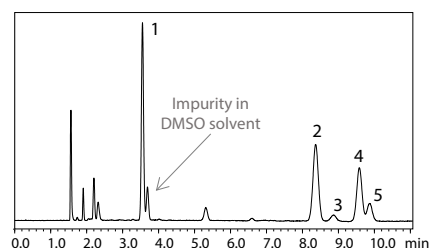

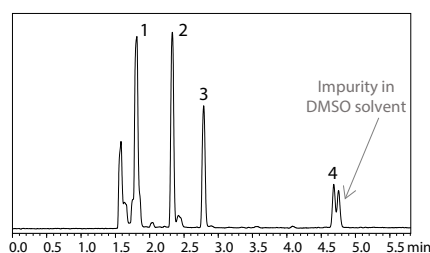**Fig. 1 Chromatogram of Class 1 Standard Solution by Procedure A (Water-Insoluble Sample)**

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 JP17 Supplement II 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, JP17 Supplement II 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

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.
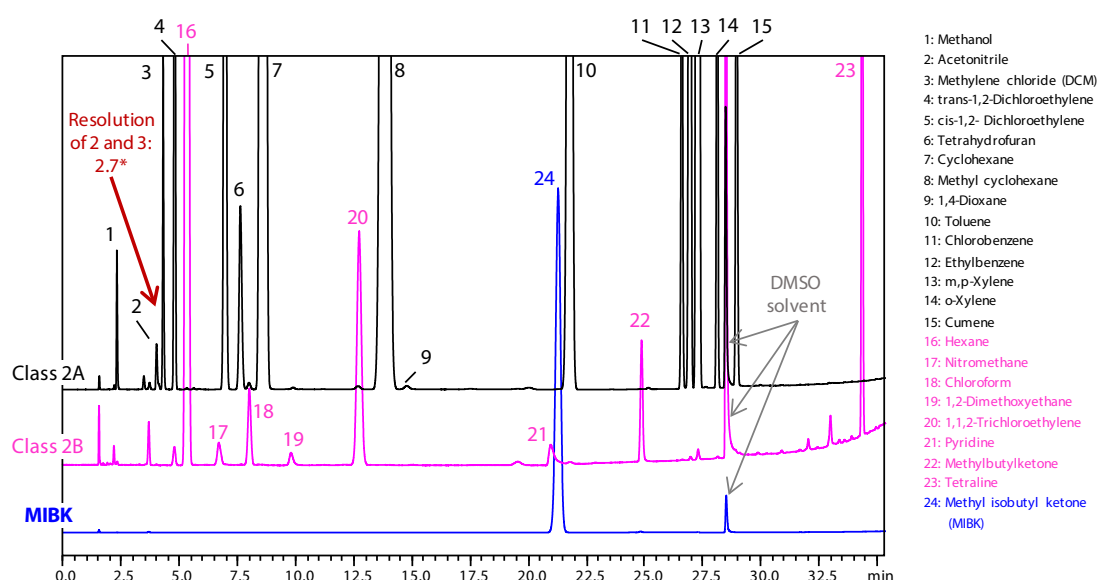

1: Methanol
2: Acetonitrile
3: Methylene chloride (DCM)
4: trans-1,2-Dichloroethylene
5: cis-1,2- Dichloroethylene
6: Tetrahydrofuran
7: Cyclohexane
8: Methyl cyclohexane
9: 1,4-Dioxane
10: Toluene
11: Chlorobenzene
12: Ethylbenzene
13: m,p-Xylene
14: o-Xylene
15: Cumene
16: Hexane
17: Nitromethane
18: Chloroform
19: 1,2-Dimethoxyethane
20: 1,1,2-Trichloroethylene
21: Pyridine
22: Methylbutylketone
23: Tetraline
24: Methyl isobutyl ketone (MIBK)

Resolution of 2 and 3: 2.7*

DMSO solvent

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

1: Cyclohexane
2: Methyl cyclohexane
3: trans-1,2-Dichloroethylene +Tetrahydrofuran
4: Methanol
5: Methylene chloride (DCM)
6: cis-1,2- Dichloroethylene
7: Acetonitrile
8: Toluene
9: 1,4-Dioxane
10: Ethylbenzene
11: p-Xylene
12: m-Xylene
13: Cumene
14: o-Xylene
15: Chlorobenzene
16: Hexane
17: 1,2-Dimethoxyethane
18: 1,1,2-Trichloroethylene
19: Chloroform
20: Methylbutylketone
21: Nitromethane
22: Pyridine
23: Tetraline
24: Methyl isobutyl ketone (MIBK)
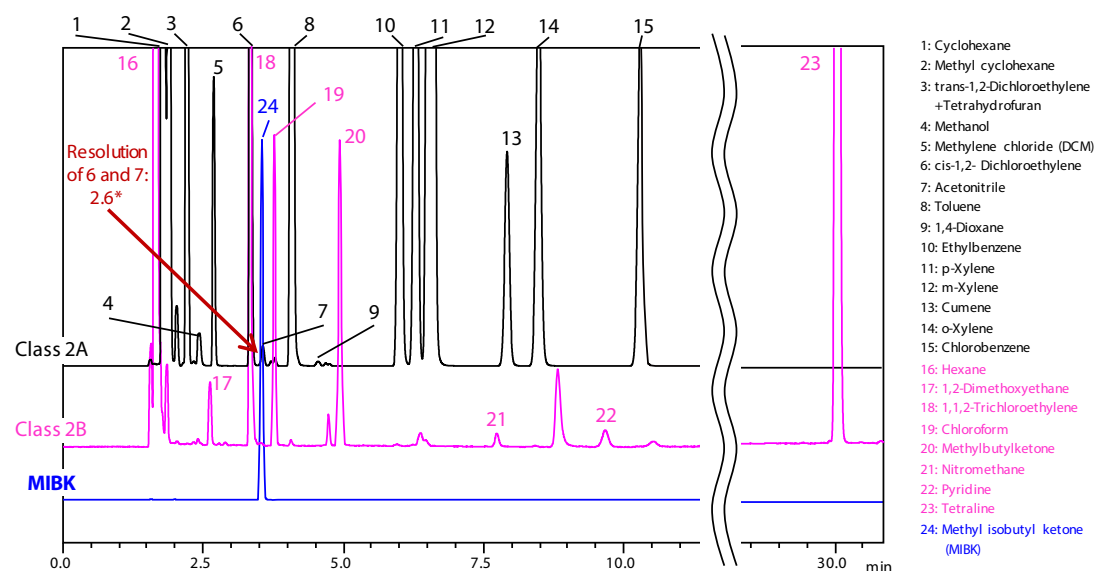
Resolution of 6 and 7: 2.6*

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

Nexis is a trademark of Shimadzu Corporation in Japan and/or other countries.
Rxi and Stabilwax are either trademarks or registered trademarks of Restek Corporation in the United States and/or other countries.

SHIMADZU

Shimadzu Corporation
www.shimadzu.com/an/