

# Application News

## No. G326B

### Gas Chromatography

## Analysis of Residual Solvents in Pharmaceuticals by Water-Insoluble Samples Using N<sub>2</sub> Carrier (JP18, USP 467)

The Japanese Pharmacopoeia 18<sup>th</sup> Edition (JP18) and the United States Pharmacopoeia (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<sub>2</sub> 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<sub>2</sub> 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 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-I-624Sil MS (0.53 mm I.D. × 30 m, d.f.= 3 μm) <sup>*2</sup> B) SH-PolarWax (0.32 mm I.D. × 30 m, d.f.= 0.25 μm) <sup>*2</sup>
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 <sub>2</sub> )
Linear velocity	: 35 cm/sec
Detector temp.	: 250 °C
FID H <sub>2</sub> flow rate	: 32 mL/min
FID make up flow rate	: 24 mL/min (N <sub>2</sub> )
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

\*1 P/N: 227-36078-01

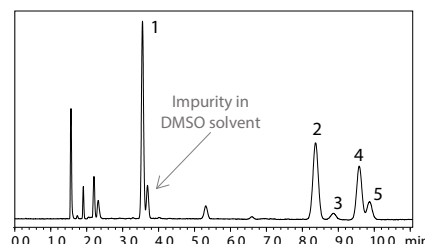
\*2 P/N: 221-75972-30

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

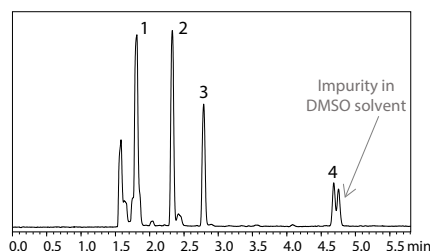
Fig. 1 and 2 show the analysis results for Procedure A and B respectively. Table 2 and 3 show the S/N ratios and the repeatability of the two procedures respectively.

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 <sup>*1</sup>	%RSD (n=6) <sup>*1</sup>
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

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

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

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

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

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

## ■ 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<sub>2</sub> carrier gas, the analysis achieved the accuracy levels required by Japanese Pharmacopoeia 18<sup>th</sup> 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<sub>2</sub> as the carrier gas were satisfactory and comparable to those with He as the carrier gas.

For information about using a H<sub>2</sub> carrier for analysis of residual solvents in pharmaceuticals using water-insoluble samples, refer to Application News 01-00177-EN.

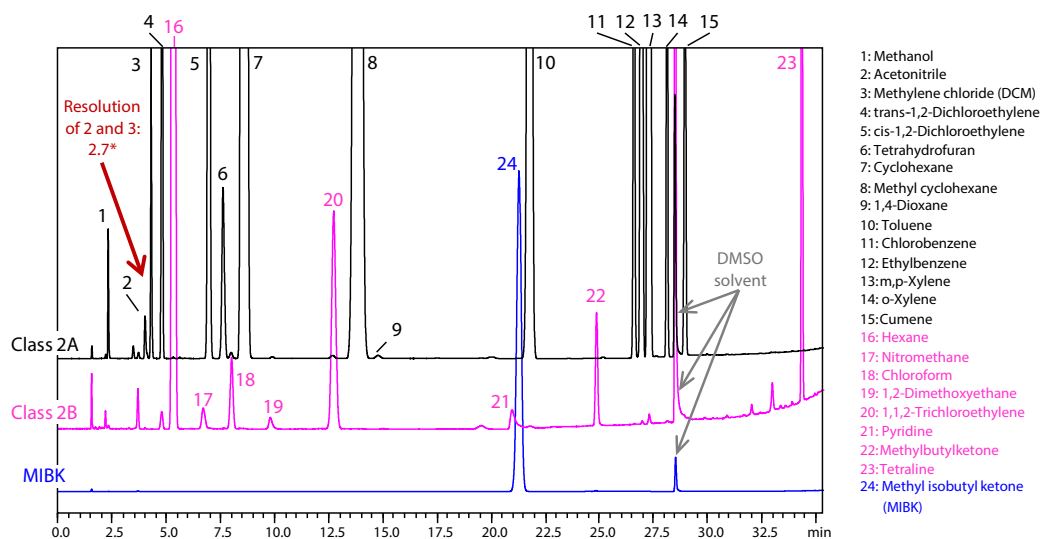


Fig. 3 Chromatogram of Class 2 Standard Solution by Procedure A (Water-Insoluble Sample)

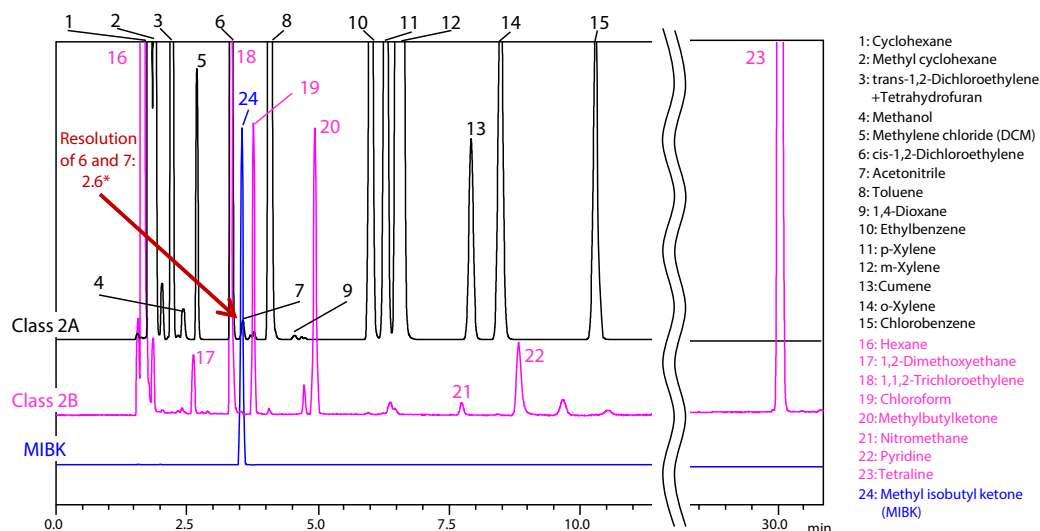


Fig. 4 Chromatogram of Class 2 Standard Solution by Procedure B (Water-Insoluble Sample)

Nexis is a trademark of Shimadzu Corporation or its affiliated companies in Japan and/or other countries.



Shimadzu Corporation

[www.shimadzu.com/an/](http://www.shimadzu.com/an/)

For Research Use Only. Not for use in diagnostic procedures.

This publication may contain references to products that are not available in your country.

Please contact us to check the availability of these products in your country.

The content of this publication shall not be reproduced, altered or sold for any commercial purpose without the written approval of Shimadzu.

See <http://www.shimadzu.com/about/trademarks/index.html> for details.

Third party trademarks and trade names may be used in this publication to refer to either the entities or their products/services, whether or not they are used with trademark symbol "TM" or "®".

Shimadzu disclaims any proprietary interest in trademarks and trade names other than its own.

The information contained herein is provided to you "as is" without warranty of any kind including without limitation warranties as to its accuracy or completeness. Shimadzu does not assume any responsibility or liability for any damage, whether direct or indirect, relating to the use of this publication. This publication is based upon the information available to Shimadzu on or before the date of publication, and subject to change without notice.

First Edition: Jun. 2020

Revision A: Jul. 2021

Revision B: Mar. 2023

➤ Please fill out the survey

## Related Products

Some products may be updated to newer models.



➤ Nexis™ GC-2030  
Gas Chromatograph

## Related Solutions

➤ Life Science

➤ Price Inquiry

➤ Product Inquiry

➤ Technical Service /  
Support Inquiry

➤ Other Inquiry