

**Analysis of Residual Solvents in Pharmaceuticals
by Nexis™ GC-2030 + HS-20
(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 and are strictly controlled.

The list of residual solvents is continuously reviewed and methylisobutylketone (MIBK) has been newly added to JP17 Supplement II in 2019. The compound is classified as Class 2 mixture A standard solution (Class 2A) in the USP.

In this article, MIBK was analyzed and its chromatogram was overlaid with that of Class 2A as a reference.

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■ **Analysis Conditions**

Shimadzu HS-20 headspace gas sampler was connected to Nexis GC-2030 gas chromatograph and used to measure Class 2A and MIBK standard solutions as described in JP17 Supplement II. As the standard solutions, water-soluble and water-insoluble samples were prepared and measured by Procedure A and B, which employ different types of columns, column temperatures, and split ratios. Table 1 and 2 below list the analysis conditions for water-soluble and water-insoluble samples respectively.

■ **Water-Soluble Samples – Analysis of Class 2A and MIBK Standard Solution**

Fig. 1 and 2 show the analysis results by Procedure A and B respectively. (Black: Class 2A, Pink: MIBK)

* The resolutions in the Fig. 1 and 2 are reference values and not guaranteed.

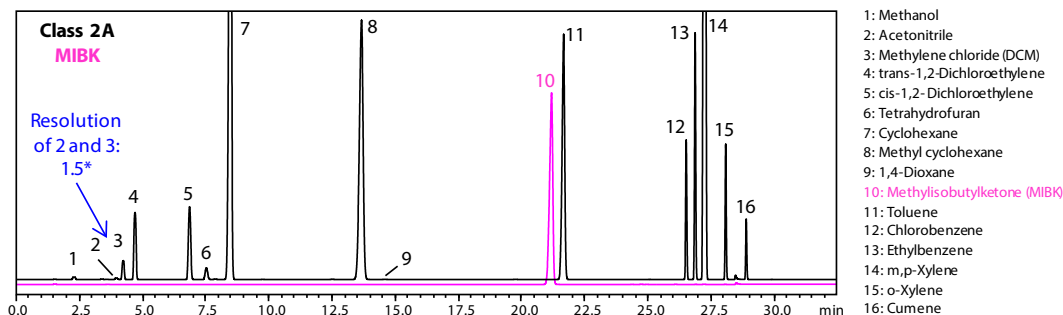


Fig. 1 Chromatogram of Class 2A and MIBK Standard Solution by Procedure A (Water-Soluble Sample)

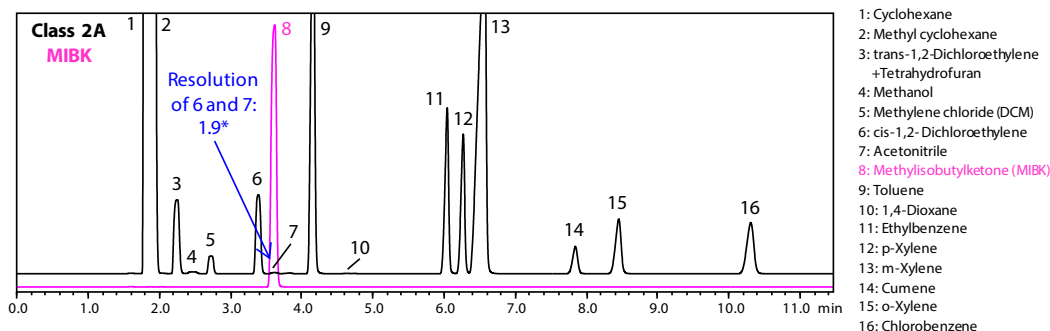


Fig. 2 Chromatogram of Class 2A and MIBK Standard Solution by Procedure B (Water-Soluble Sample)

■ **Water-Insoluble Samples – Analysis of Class 2A and MIBK Standard Solution**

Fig. 3 and 4 show the analysis results by Procedure A and B respectively. (Black: Class 2A, Pink: MIBK)

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

Conclusion

Methylisobutylketone (MIBK), the newly added to JP17 Supplement II, was analyzed in water-soluble and water-insoluble samples with sufficient sensitivity by both Procedure A and B. Although MIBK was separated from the rest of Class 2A components in the chromatogram by Procedure A, it co-eluted with acetonitrile by Procedure B.

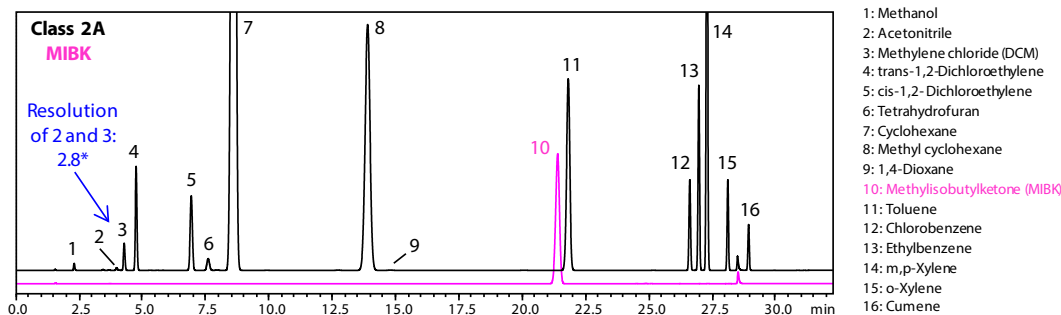


Fig. 3 Chromatogram of Class 2A and MIBK Standard Solution by Procedure A (Water-Insoluble Sample)

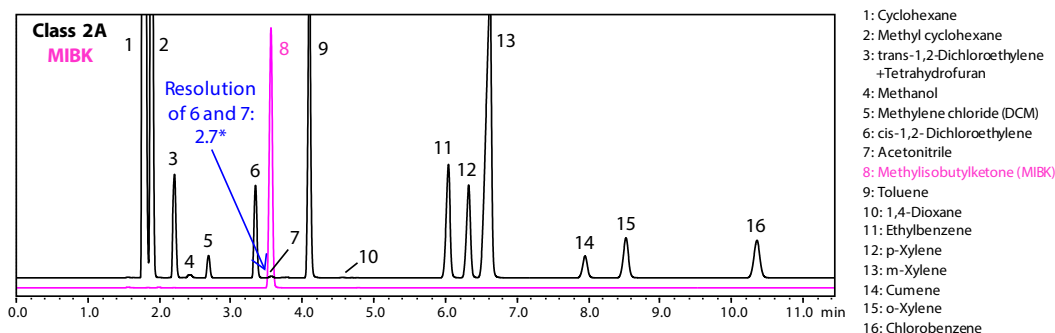


Fig. 4 Chromatogram of Class 2A and MIBK Standard Solution by Procedure B (Water-Insoluble Sample)

Table 1 Analysis Conditions – Water-Soluble Samples

GC analysis conditions (Procedure A and B)	
Model	: Nexis™ GC-2030
Detector	: FID-2030 flame ionization detector
Column	: A) SH-Rxi™-624 Sil MS (0.32 mm I.D. × 30 m, d.f.= 1.8 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 (He) 35 cm/sec
Detector temp.	: 250 °C
Detector gas	: H ₂ 32 mL/min, Air 200 mL/min
Make up	: 24 mL/min (He)
Injection volume	: 1 mL
HS-20 analysis conditions (same for Procedure A and B)	
Oven temp.	: 80 °C
Sample line temp.	: 110 °C
Transfer line temp.	: 120 °C
Vial volume	: 20 mL
Vial heat-retention time	: 60 min
Vial pressurization time	: 1 min
Vial pressure	: 75 kPa
Loading time	: 0.5 min
Needle flush time	: 5 min

Table 2 Analysis Conditions – Water-Insoluble Samples

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 (He) 35 cm/sec
Detector temp.	: 250 °C
Detector gas	: H ₂ 32 mL/min, Air 200 mL/min
Make up	: 24 mL/min (He)
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 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

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