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Application Data Sheet

No.90

GC-MS
Gas Chromatograph Mass Spectrometer

Analysis of Impurities in Tests for Residual Solvents in Pharmaceuticals Using GC-MS

The HS-GC-FID method is adopted for tests of residual solvents in pharmaceuticals, but GC-MS is effective for confirming any unknown peaks (impurities) detected in such tests.
United States Pharmacopoeia (USP) 467 is well known as a test method for residual solvents in pharmaceuticals. In this method, analysis is performed using analysis columns with an internal diameter of 0.32 mm or 0.53 mm, and a length of 30 m, at a linear velocity of 35 cm/s. When GC-MS is used to confirm unknown peaks in chromatograms obtained by GC-FID analysis using large bore columns, approximating the retention times in both chromatograms is essential. If the linear velocity is set at 35 cm/s with GC-MS, the retention times are roughly approximated. However, using such large bore columns and a linear velocity of 35 cm/s in GC-MS will prevent analysis under the designated USP conditions for several reasons. For example, the flowrate will be large, which will have an impact on sensitivity, and the inlet pressure will exceed the control range (decompression region) due to the vacuum in the MS section. With its differential vacuum system, the GCMS-QP2010 Ultra features high vacuum efficiency, enabling analysis using the same 0.53 mm analysis columns as in GC-FID. The linear velocity of 35 cm/s designated in USP 467 can be achieved by connecting the optimal resistance tube to the column outlet.
This Data Sheet presents an example of the analysis of unknown peaks in a test for residual solvents in pharmaceuticals, using analysis columns that complies with USP467 Procedure A for residual solvents, utilizing the Shimadzu HS-20 Trap headspace sampler, which features a trapping function, and the GCMS-QP2010 Ultra.

Analysis Conditions

The analysis conditions are shown in Table 1.
To achieve control at low linear velocities with a large bore column, a resistance tube was connected to the column outlet. The optimal resistance tube size was configured by referring to the backflush setting software.

Table 1 Analysis Conditions

Headspace Sampler:	HS-20 Trap		
GC-MS:	GCMS-QP2010 Ultra		
[HS-20]			
Mode:	Loop (1 mL)		
Vial Warming:	80 °C	Vial Warming Time:	60 min
Vial Agitation:	Off		
Vial Pressurization:	75 kPa		
Vial Pressurization Time:	3.0 min	Pressure Equilibration Time:	0.1 min
Load Time:	0.5 min	Load Equilibration Time:	0.1 min
Injection Time:	45 min	Needle Flash Time:	45 min
Sample Line Temp.:	150 °C	Transfer Line Temp.:	150 °C
[GC]			
Columns:	Rxi®-624sil MS, 30 m × 0.53 mm I.D., d.f. 3.0 µm + resistance tube 0.82 m × 0.18 mm I.D. *1 Rxi®-624sil MS, 30 m × 0.32 mm I.D., d.f. 1.8 µm + resistance tube 1.45 m × 0.18 mm I.D.		
Column Temp.:	40 °C (20 min) – 10 °C/min – 240 °C (20 min)		
Control Mode:	Pressure (He)	0.53 mm column: 25.0 kPa (20 min) – -0.8 kPa/min – 9.0 kPa (5 min) 0.32 mm column: 69.8 kPa (20 min) – 3.0 kPa/min – 129.8 kPa (5 min)	
Injection Mode:	Split (split ratio 5)		
[MS]			
Ion Source Temp.:	200 °C	Interface Temp.:	250 °C
Measurement Mode:	Scan	Scan Range:	29 - 250 *m/z*
Event Time: 0.2 sec			
Ionization Voltage:	70 V		

*1: A resistance tube (PN 10046, Shimadzu GLC) was cut at the optimal length, and then connected using a capillary column press-tight connector (PN 221-38102-91). The length of the resistance tube shown here is only an example, and may change depending on the analysis column lot.

(1) Sample Analysis using a 30 m Column with an Internal Diameter of 0.53 mm

Figs. 1 and 2 show the GC-MS results of measuring a Class 2 Residual Solvents Standard Solution (water-soluble articles) using a 30 m column with an internal diameter of 0.53 mm, to compare them to the results obtained from separate measurements by GC-FID. With a 30 m × 0.53 mm I.D. column, the column outlet pressure will be negative, so the flowrate designated in Procedure A cannot be set. Here, the linear velocity of 35 cm/s designated in Procedure A was achieved by connecting an 82 mm × 0.18 mm I.D. resistance tube to the column outlet, and a chromatogram pattern approximating the GC-FID results was obtained. The column flowrate with GC-MS was calculated at 4.86 mL/min, but measurements were not a problem for the GCMS-QP2010 Ultra, with its high vacuum efficiency.

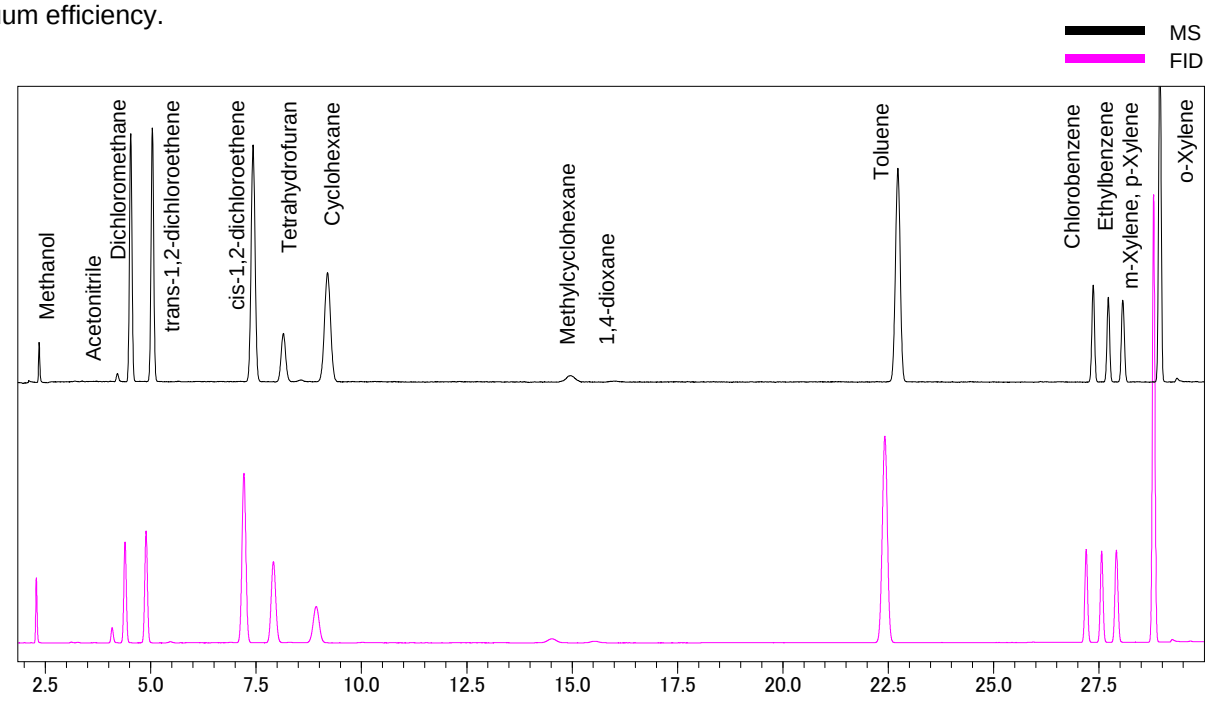

Fig. 1 Chromatogram Comparison (Internal Diameter 0.53 mm, Class 2A)

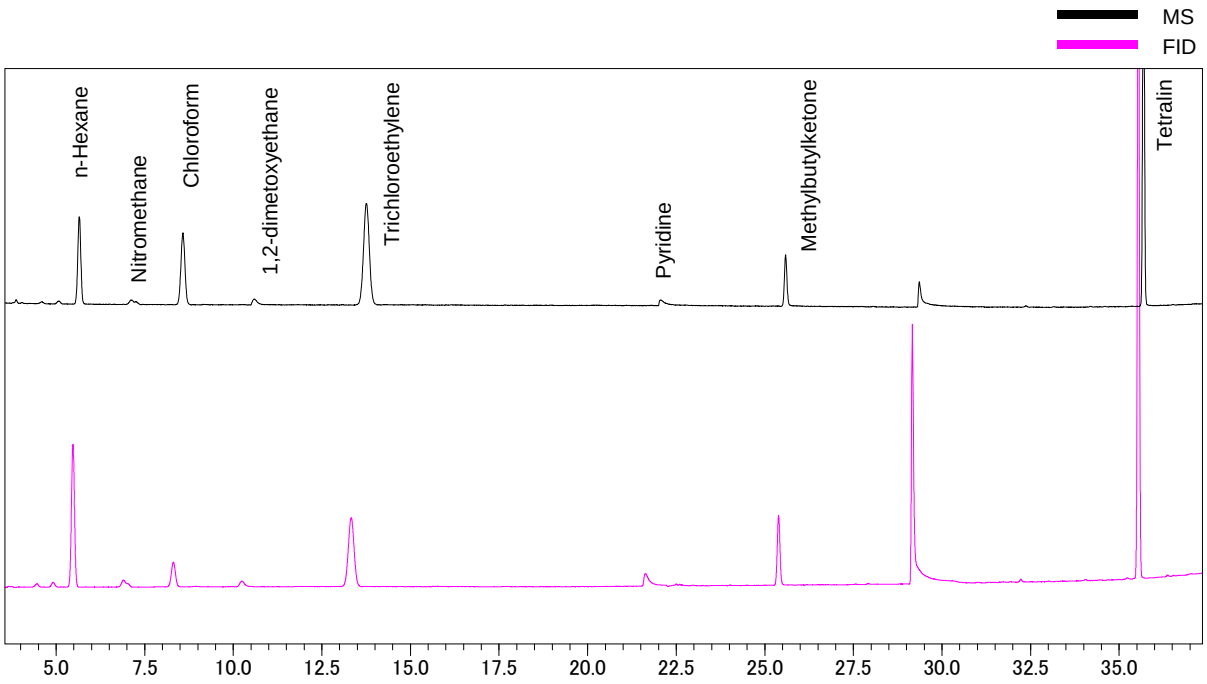

Fig. 2 Chromatogram Comparison (Internal Diameter 0.53 mm, Class 2B)

(2) Sample Analysis Using a 30 m Column with an Internal Diameter of 0.32 mm

Figs. 3 and 4 show the results of measuring a Class 2 Residual Solvents Standard Solution (water-soluble articles) using a 30 m column with an internal diameter of 0.32 mm. With the 0.32 mm I.D. column, measurements can be performed with GC-MS if the linear velocity is set at 40 cm/s or higher. However, the retention time will differ significantly from that for GC-FID measured under the designated USP conditions. Here, the linear velocity of 35 cm/s designated in Procedure A was achieved by connecting an 145 mm × 0.18 mm I.D. resistance tube to the column outlet, and a chromatogram pattern approximating the GC-FID results was obtained.

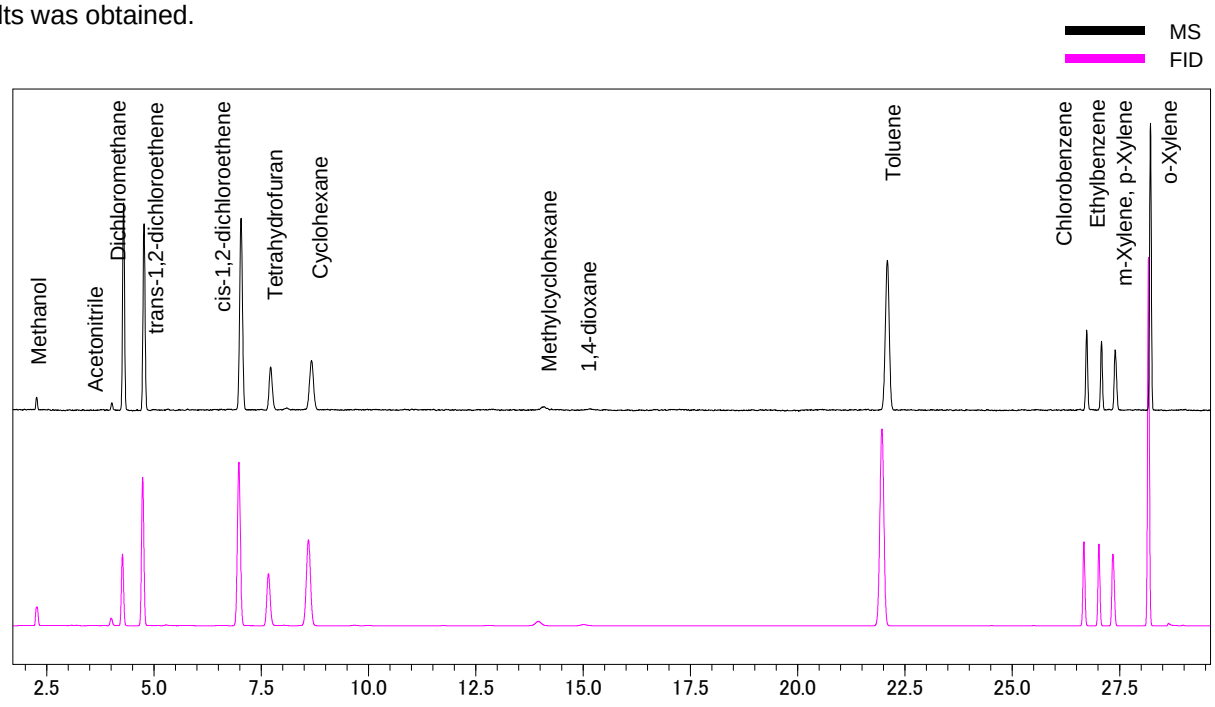

Fig. 3 Chromatogram Comparison (Internal Diameter 0.32 mm, Class 2A)

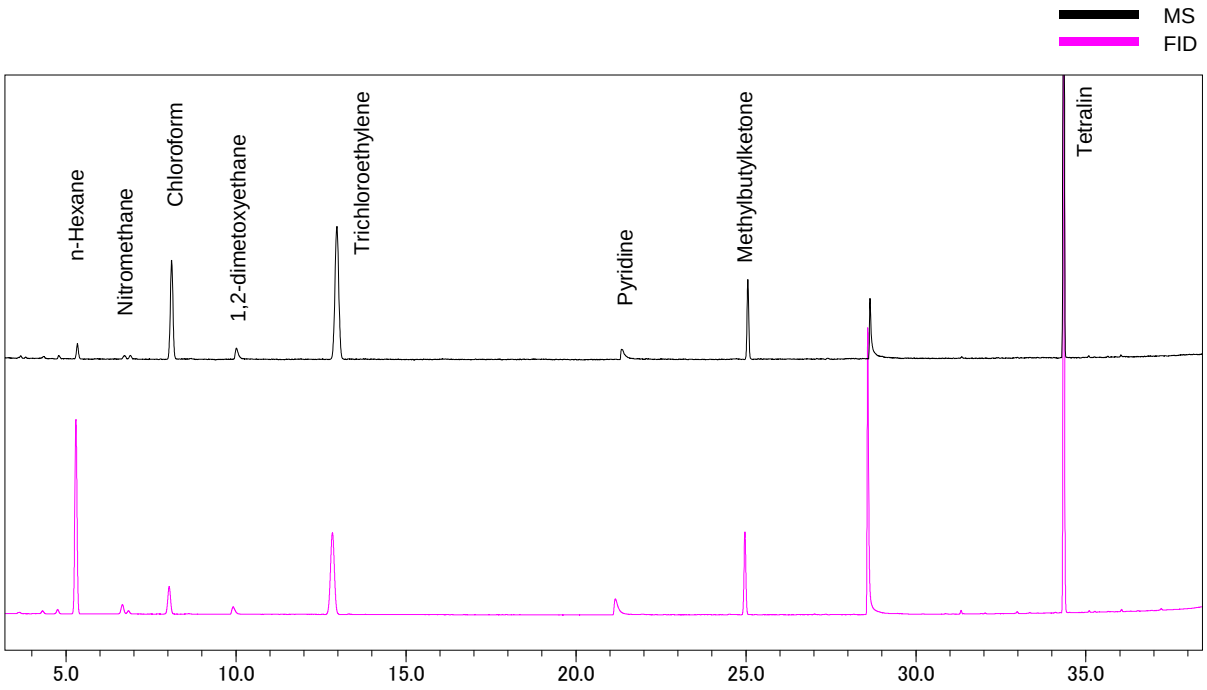

Fig. 4 Chromatogram Comparison (Internal Diameter 0.32 mm, Class 2B)

(3) A Sample Impurity Analysis

Fig. 5 shows an example of the measurement of a commercially available pharmaceutical drug test solution using a 30 m × 0.53 mm I.D. column. The peaks ((1) and (2)) not contained in Standard Solutions Class 1, 2A, and 2B were confirmed in both the FID and MS results. They were inferred from the mass spectra to be n-Butanol and Butylacetate, target components in Class 3. When trap injection (5 cycle extraction) was performed, peak A, which was essentially undetectable with loop FID and GCMS analysis, was detected with high sensitivity, and was identified as Ethyl Acetate (Fig. 6). Accordingly, use of the HS-20 and GCMS-QP2010 Ultra evidently simplifies the analysis of unknown peaks in tests for residual solvents in pharmaceuticals.

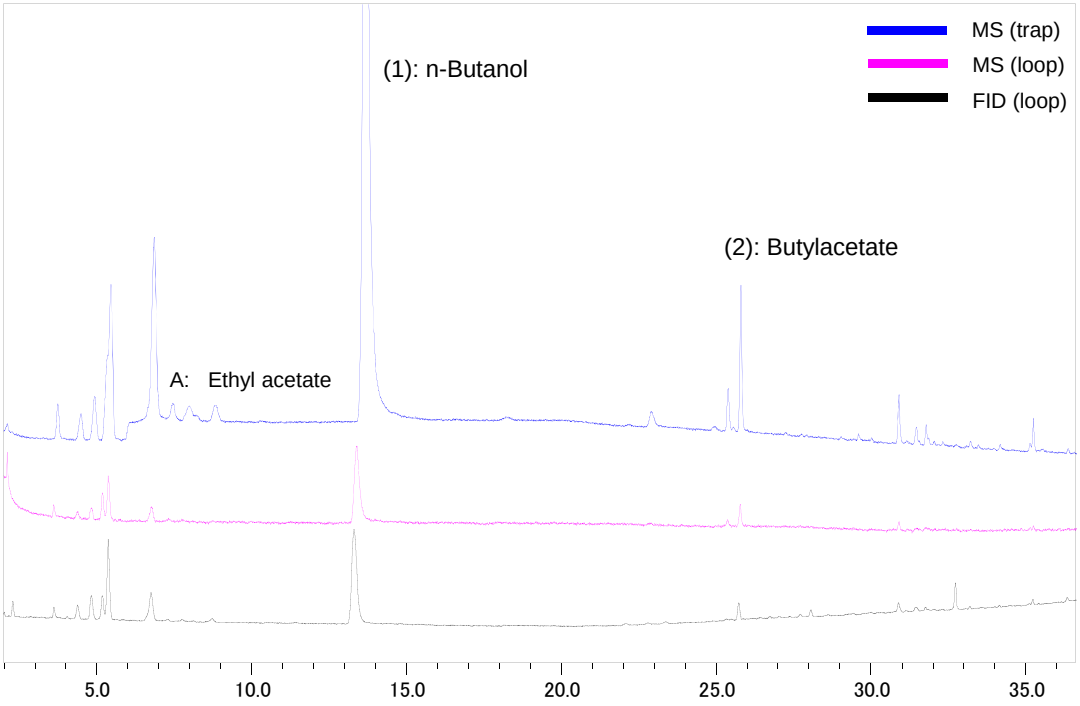

Fig .5 Test Solution Chromatograms

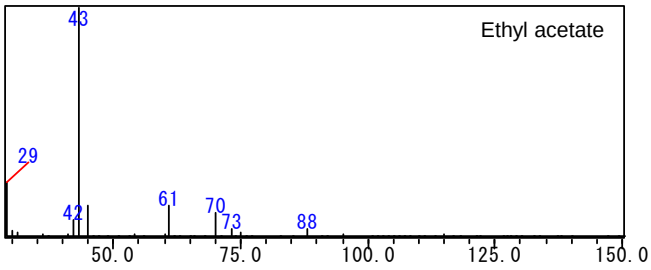

Fig. 6 Mass Spectrum for Peak A

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