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Application News

No.M272

Gas Chromatography Mass Spectrometry

Analysis of Residual Solvents in Pharmaceuticals Using Headspace GC-FID/MS Detector Splitting System

Headspace gas chromatography with flame ionization detection (GC-FID) is often used for residual solvent testing of pharmaceuticals, though the qualitative power of this method is not particularly high. Because gas chromatography mass spectrometry (GC/MS) utilizes MS to perform qualitative analysis based on mass spectra, GC/MS can be used to estimate and identify individual peaks detected in the expected vicinity of a target solvent as well as other unknown peaks.
We describe an example of residual solvent test of a pharmaceutical using a detector splitting system that simultaneously obtains FID and MS data in a single measurement.

Sample Preparation

According to Water-Soluble Articles, Procedure A, in USP <467>, we prepared a class 1 standard solution, class 2 standard solution A, class 2 standard solution B, test solution, and class 1 system suitability solution. An active pharmaceutical ingredient was used for the test solution sample.

Analytical Conditions

The image of the Shimadzu GCMS-QP2020/FID detector splitting system is shown in Fig. 1, and analytical conditions are shown in Table 1. Headspace conditions were determined based on USP <467>. The column outlet was split between FID and MS, and MS was performed in scanning mode. Using Shimadzu's Advanced Flow Technology Software to determine the splitting ratio, the flowrate ratio was optimized to FID:MS of 1:1.

Table 1 Analytical Conditions

Headspace Sampler	: HS-20
GCMS	: GCMS-QP2020
Hydrogen Flame Ionization Detector Splitting System	: FID-2010Plus
HS	
Mode	: Loop (volume 1 mL)
Oven Temp.	: 80 °C
Sample Line Temp.	: 90 °C
Transfer Line Temp.	: 105 °C
Gas Pressure for Vial Pressurization	: 76.4 kPa
Vial Equilibrating Time	: 45 min
Vial Pressurizing Time	: 2.0 min
Pressure Equilibrating Time	: 0.1 min
Load Time	: 0.5 min
Load Equilibrating Time	: 0.1 min
Injection Time	: 0.5 min
Needle Flushing Time	: 15.0 min
APC Pressure	: 20 kPa
GC	
Column	: SH Rxi-624sil MS (30 m × 0.32 mm I.D., 1.8 µm)
Injection Mode	: Split (split ratio 1:5)
Control Mode	: Constant Pressure (89.4 kPa)
Carrier Gas	: He
Oven Temp.	: 40 °C (20 min) → 10 °C/min → 240 °C (20 min)
Restrictor (FID)	: 1.1 m × 0.25 mm
Restrictor (MS)	: 1.5 m × 0.20 mm
APC Pressure	: 20 kPa
FID	
Temp.	: 250 °C
Make-Up Flowrate	: 30 mL/min (He)
Hydrogen Flowrate	: 40 mL/min
Air Flowrate	: 400 mL/min
MS	
Ion Source Temp.	: 200 °C
Interface Temp.	: 250 °C
SCAN Range	: *m/z* 29 to 250
Event Time	: 0.3 sec

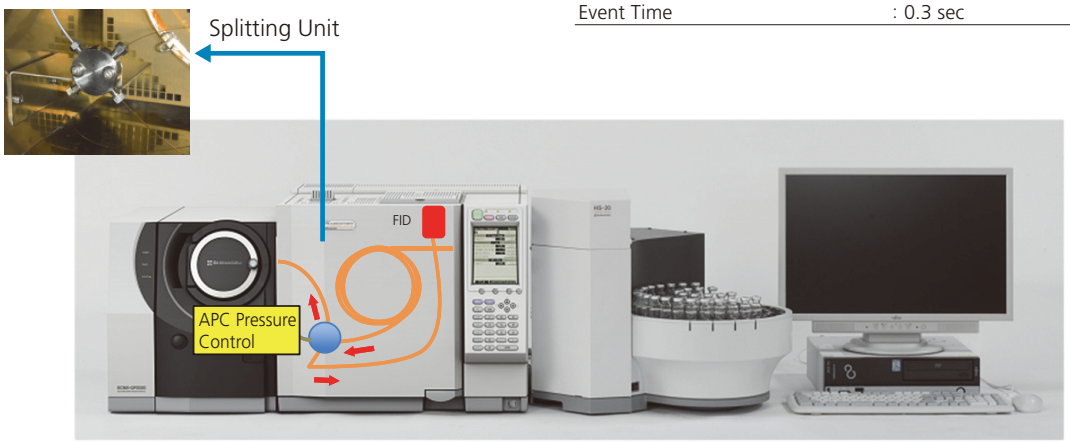

Fig. 1 System Image

Results

Fig. 2 to 5 show the FID and MS chromatograms obtained for class 1 standard solution, class 2 standard solution A, class 2 standard solution B, and class 1 system suitability solution.

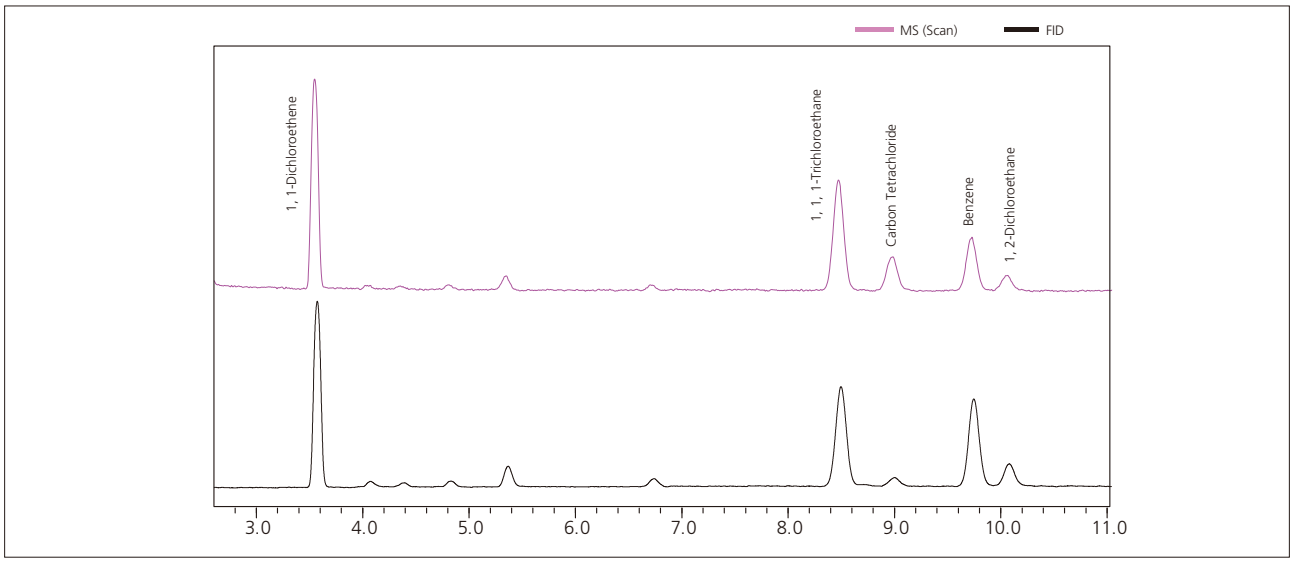

Fig. 2 Chromatograms of Class 1 Standard Solution

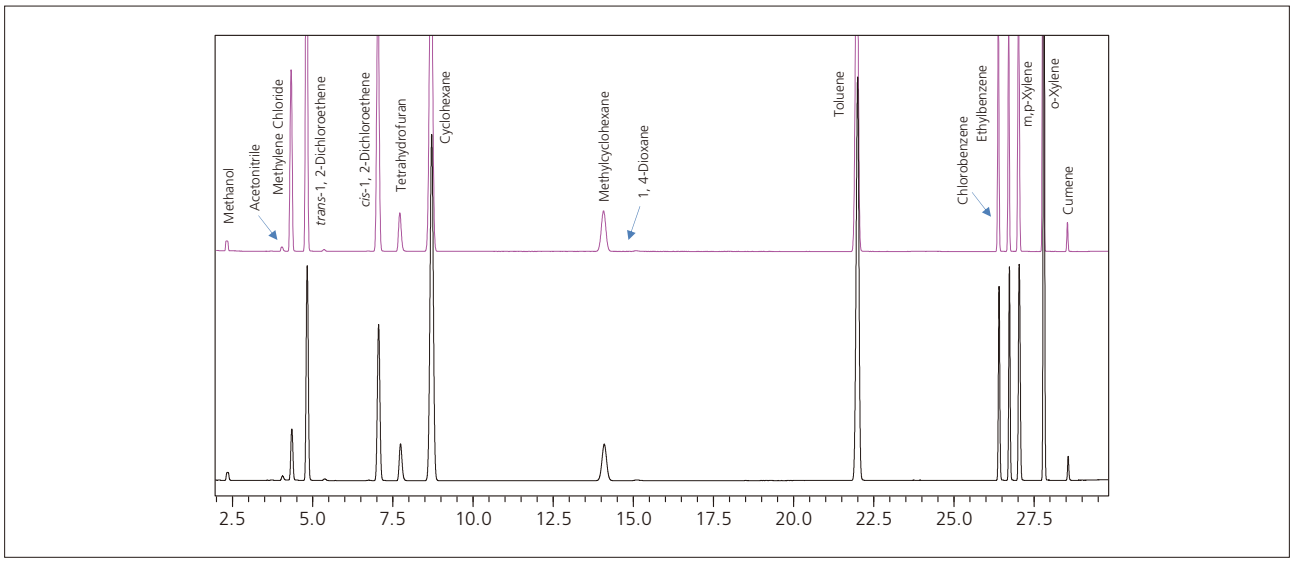

Fig. 3 Chromatograms of Class 2 Mixture A Standard Solution

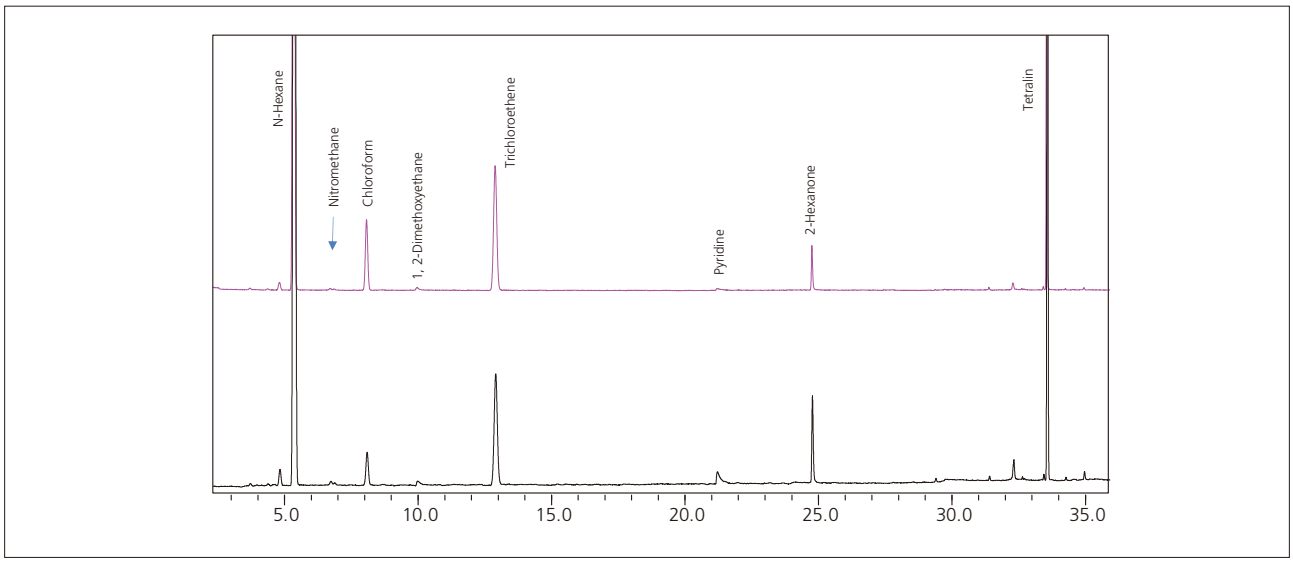

Fig. 4 Chromatograms of Class 2 Mixture B Standard Solution

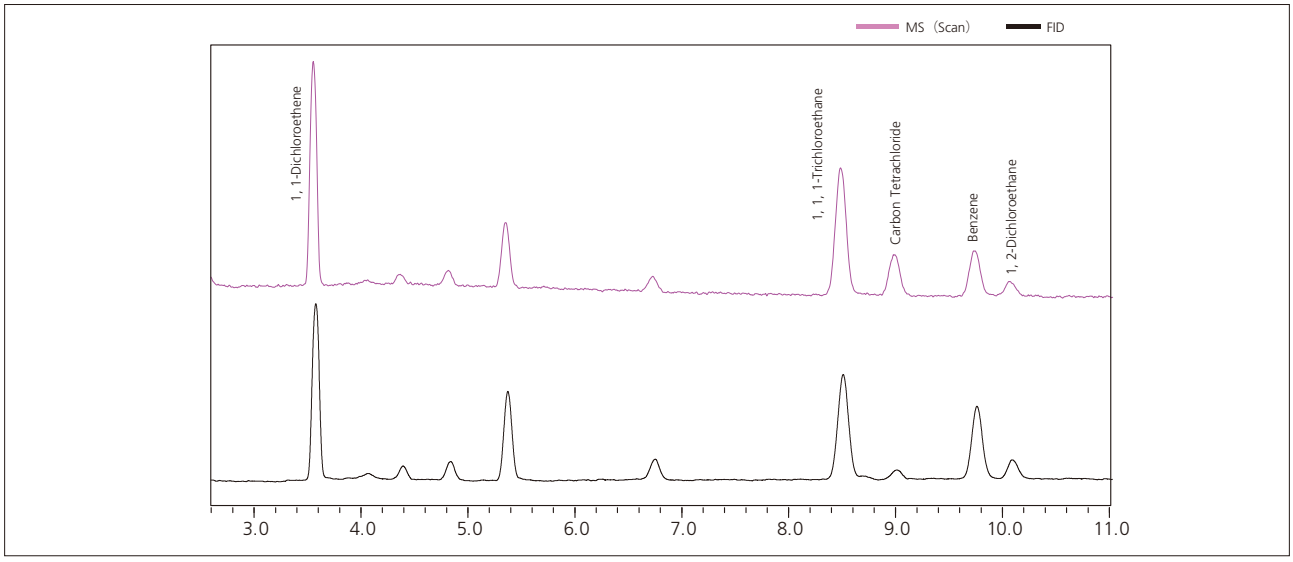

Fig. 5 Chromatograms of Class 1 System Suitability Solution

To check the mass spectra of the peaks detected by FID, the peak retention times in chromatograms obtained by FID and MS must match as closely as possible. Looking at Fig. 2 to 4 show all the peak retention times are lined up, from the earliest to the latest constituent.
When using a detector splitting system, the two detectors must detect the same peaks detected by normal gas chromatography. In other words, detector splitting systems are expected to have the equivalent system performance as a normal analytical system. Procedure A in USP <467> states the two items below concerning system suitability. We attempted to confirm the two items below for the detector splitting system, and for the repeatability of class 1 standard solution analysis.

(1) Detector confirmation
The S/N ratio of 1, 1, 1-trichloroethane in class 1 standard solution is 5 or higher; the S/N ratio of each peak in class 1 system suitability solution is 3 or higher.

(2) System performance
The peak resolution between acetonitrile and dichloromethane in class 2 standard solution is 1.0 or higher.

The results (FID S/N ratios) of analyzing class 1 standard solution and class 1 system suitability solution with the detector splitting system are shown in Table 2, and the repeatability results (FID repeatability) of analyzing class 1 standard solution are shown in Table 3. These results show the detector splitting system meets the performance required of a standard system. The peak resolution of acetonitrile and dichloromethane in class 2 standard solution was 2.37, showing this system is also suitable in terms of resolution.

Table 2 Signal-to-Noise Ratio in Class 1 Standard Solution and System Suitability Solution

Compound	Standard solution	Solution for system suitability test
1, 1-Dichloroethene	221.9	141.4
1, 1, 1-Trichloroethane	117.6	82.2
Carbon tetrachloride	10.2	7.6
Benzene	106.3	56.8
1, 2-Dichloroethane	26.4	14.2

Table 3 Repeatability in Class 1 Standard Solution (n=6)

Compound	Relative standard deviation (%)
1, 1-Dichloroethene	1.6
1, 1, 1-Trichloroethane	2.2
Carbon tetrachloride	1.8
Benzene	3.5
1, 2-Dichloroethane	2.9

The results (chromatograms) of analyzing active pharmaceutical ingredients in the detector splitting system are shown in Fig. 6, and the mass spectra of detected peaks are shown in Fig. 7 to 9. Peaks a and b, based on their respective mass spectra (Fig. 7 and 8), were estimated to be ethyl acetate and butanol. Both these constituents are low toxicity class 3 solvents.

Though its peak strength is smaller than that observed in the standard solution, a peak was also detected at the elution position of o-xylene (c). Checking the mass spectrum of this peak (Fig. 9) showed it differed from the mass spectrum of xylene (peak d, Fig. 10), and was estimated to be dibutyl ether.

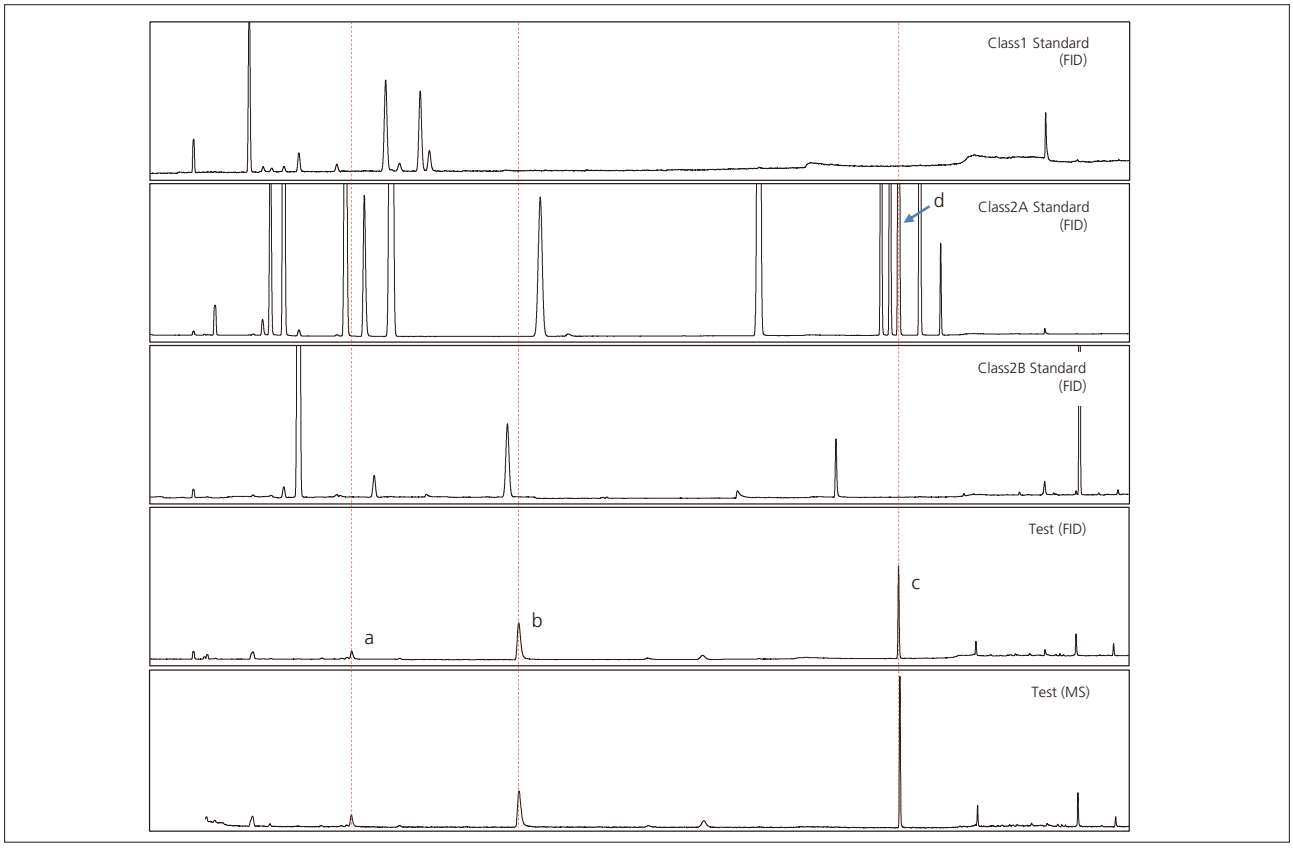

Fig. 6 Chromatograms of Standard Solutions and Test Solutions

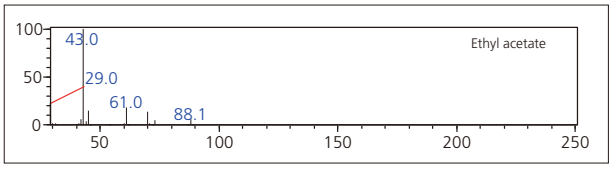

Fig. 7 Mass Spectrum of Peak a

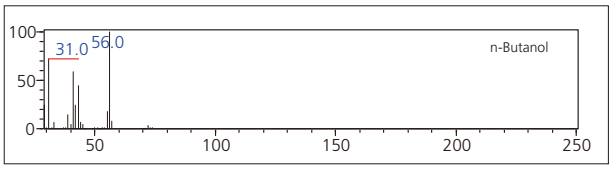

Fig. 8 Mass Spectrum of Peak b

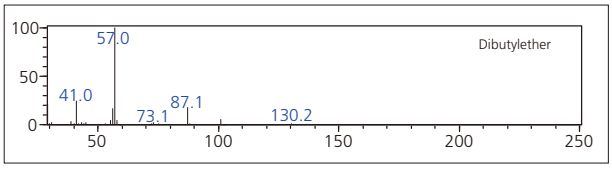

Fig. 9 Mass Spectrum of Peak c

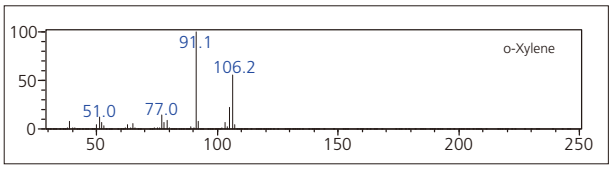

Fig. 10 Mass Spectrum of Peak d

Conclusion

An FID and MS detector splitting system obtains FID and MS data simultaneously in a single analysis, and can be used as a simpler method of confirming constituent identity. This system shows promise for use in residual solvent testing of pharmaceuticals.

Note: Reference USP <467>
This data was obtained by a method that does not conform to the pharmacopoeia, as analytical conditions based on USP <467> was modified before use.

First Edition: Jul. 2016

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