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Application News

GC HS-20 NX/Nexis™ GC-2030 /GCMS-QP 2020 NX

Qualitative Analysis Using HS-GC-FID/MS when Testing for Residual Solvents in Pharmaceuticals — JP18, USP467: Water-Soluble Samples —

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User Benefits

- Good separation was achieved for *tert*-butyl alcohol (t-BuOH) and cyclopentyl methyl ether (CPME), both recently recommended for classification as class 2 solvents in ICH Q3C (R8).
- HS-GC/MS can obtain qualitative information about unknown components that are difficult to distinguish by flame ionization detection (FID) analysis.
- LabSolutions™ DB/CS can be used to support data integrity and prevent data falsification and other similar problems.

■ Introduction

The Japanese Pharmacopoeia 18th Edition (JP18) and United States Pharmacopeia General Chapter <467> Residual Solvents describe tests for residual solvents in pharmaceuticals that are mainly performed by headspace gas chromatography coupled with flame ionization detection (HS-GC-FID). Residual solvents in pharmaceuticals are strictly controlled based on an evaluation of the risk they pose to human health and classified as Class 1, 2, or 3 solvents. Testing for these residual solvents in pharmaceuticals requires highly sensitive analytical methods. Qualitative analysis by GC-FID normally requires the use of standard reference solvents, and accurate solvent identification can be difficult when peaks overlap. However, gas chromatography-mass spectrometry (GC-MS) can also provide qualitative information about sample components based on mass spectra. Unknown peaks or peaks that are difficult to distinguish due to their proximity to other analyte peaks can be identified using mass spectrometry, or mass spectrometry can be used to investigate causes of contamination and other issues.

This article presents results from using an HS-20 NX headspace sampler and GCMS-QP2020 NX to analyze water-soluble samples of Class 1 and Class 2 solvents.

Fig. 1 GCMS-QP 2020 NX + HS-20 NX

■ Sample Preparation

A Class 1 standard solution, Class 2A standard solution, Class 2B standard solution, and test solution were prepared according to each method described under Procedure A for water-soluble samples. The Class 2A standard solution was spiked with t-BuOH and CPME, both recently recommended for classification as Class 2 solvents in ICH Q3C (R8).

■ Instrument Configuration and Analysis Conditions

An HS-20 NX headspace sampler was coupled to a GCMS-QP2020 NX (Fig. 1) and used to perform Procedure A testing of water-soluble samples based on JP18 and USP<467>. The analysis conditions are shown in Table 1. The Nexis GC-2030 was used for GC-FID analysis, and the GCMS-QP2020 NX was used for GC-MS analysis. Measurements were taken with each detector using the same column for both instruments.

Table 1 Water-Soluble Sample Analysis Conditions

GC-MS Analysis Conditions (Procedure A)	
Model	: GCMS-QP2020 NX
Column	: SH-I-624 Sil MS (0.32 mm I.D. × 30 m, d.f.= 1.8 µm)
Column Temp.	: 40 °C (20 min) – 10 °C/min – 240 °C (20 min) Total 60 min
Injection Mode	: Split 1 : 5
Carrier Gas Controller	: Constant linear velocity mode (He)
Linear Velocity	: 40 cm/sec
[FID-2030]	
Detector Temp.	: 250 °C
FID H_2 Flowrate	: 32 mL/min
FID Make-up Flowrate	: 24 mL/min (He)
FID Air Flowrate	: 200 mL/min
[MS]	
Ion Source Temp.	: 200 °C
Interface Temp.	: 250 °C
SCAN Range	: m/z 30 to 250
Event Time	: 0.3 sec
HS Analysis Conditions (Procedure A)	
Oven Temperature	: 80 °C
Equilibration Time	: 45 min
Sample Line Temp.	: 110 °C
Transfer Line Temp.	: 120 °C
Vial Stirring	: Off
Vial Volume	: 20 mL
Vial Pressurization Time	: 1 min
Vial Pressure	: 75.0 kPa (He)
Loading Time	: 0.5 min
Needle Flush Time	: 5 min
Injection Volume	: 1 mL
Load Equilib. Time	: 0 min

■ FID Analysis of a Class 1 Standard Solution

Table 2 shows the S/N ratio and reproducibility results for each compound in a Class 1 standard solution.

These results meet the acceptance criterion for Procedure A system suitability testing cited by JP18 and USP<467>: an S/N ratio of 1,1,1-trichloroethane of not less than 5, as well as the criterion cited by JP18: a relative standard deviation of each peak area of not more than 15 %.

Table 2 S/N Ratio and Reproducibility of Class 1 Standard Solution (Procedure A)

Peak No.	Compound	S/N Ratio*1	Relative standard deviation (%)*1 (n=6)
1	1,1-Dichloroethane	190	1.92
2	1,1,1-Trichloroethane	223	1.81
3	Carbon tetrachloride	12	2.61
4	Benzene	247	1.46
5	1,2-Dichloroethane	140	0.71

*1 The S/N ratio and relative standard deviation values are for reference purposes and not intended to be guaranteed values.

■ Analysis of Standard Solutions (Water-Soluble Sample)

Figures 2 to 4 show FID and MS chromatograms obtained from analyzing the Class 1 standard solution, Class 2A standard solution, and Class 2B standard solution. When verifying the mass spectra of peaks detected by FID, peak retention times should be matched as closely as possible between FID and MS chromatograms.

The results show that using the same column in both instruments and performing analysis in constant linear velocity mode allowed peak retention times to be matched for all analytes. The results also confirm the two solvents added to the Class 2A standard solution (Fig. 3: Compounds labeled in red) were separated from other analytes.

Note: The degrees of separation shown in these figures are for reference purposes and not intended to be guaranteed values.

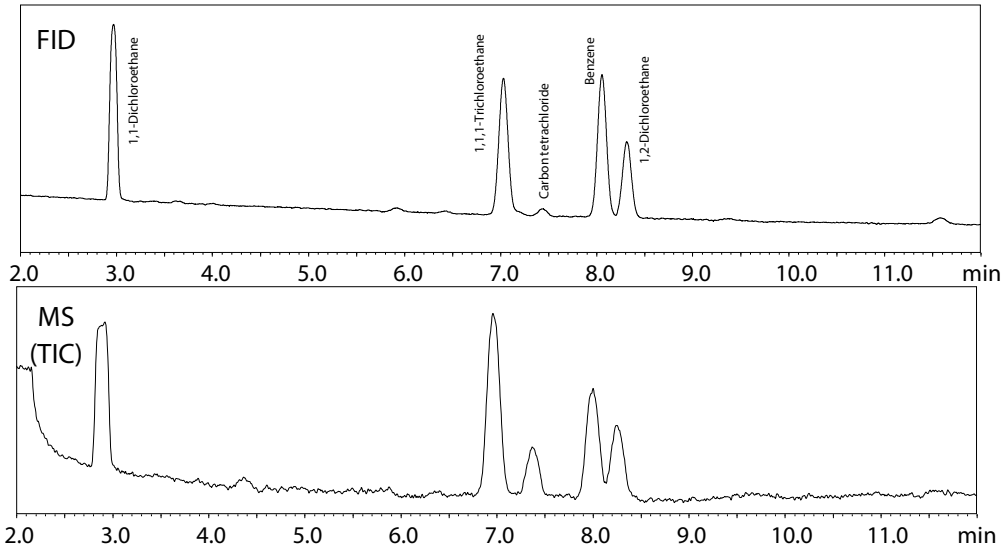

Fig. 2 Chromatogram of Procedure A Class 1 Standard Solution (Water-Soluble)

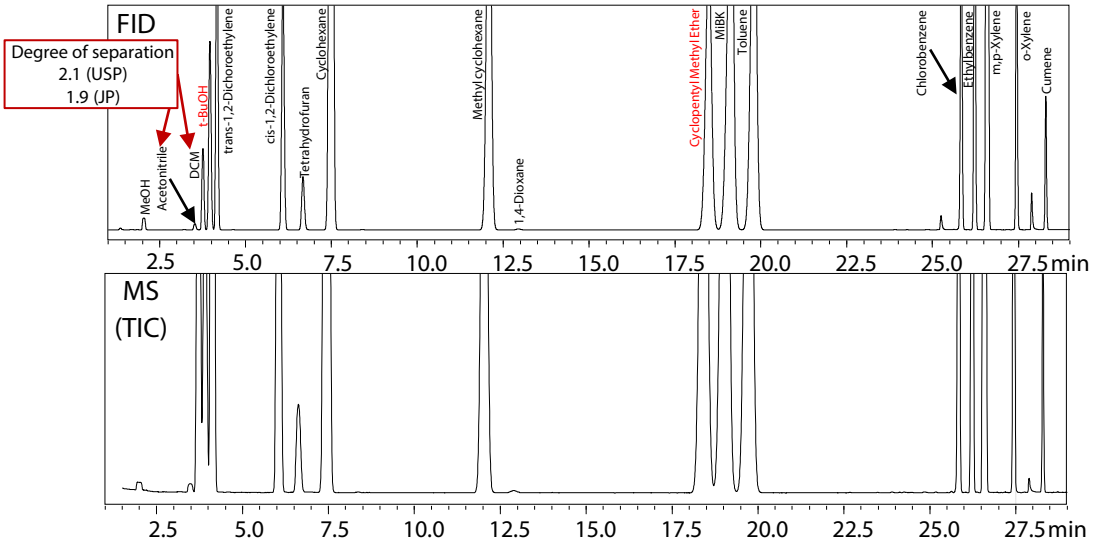

Fig. 3 Chromatogram of Procedure A Class 2A Standard Solution (Water-Soluble)

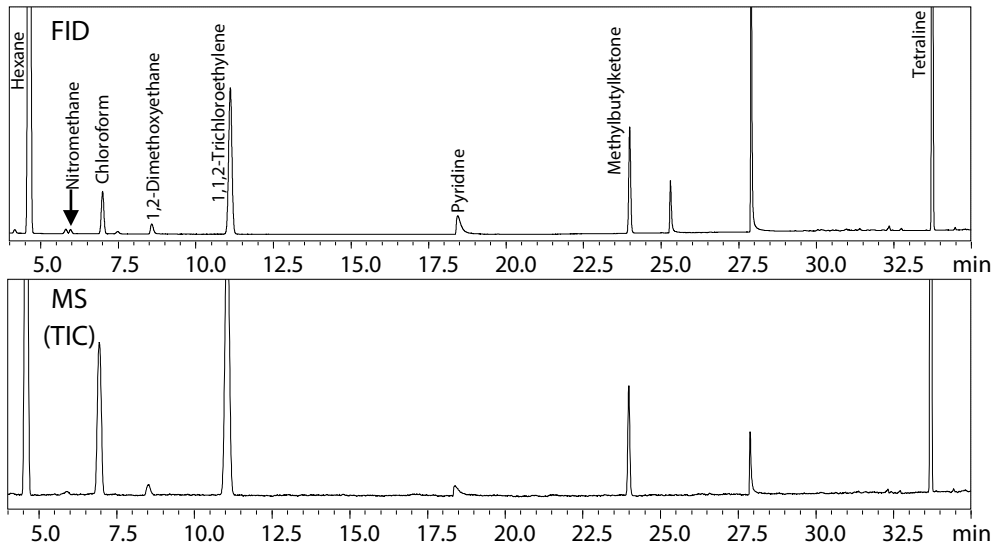

Fig. 4 Chromatogram of Procedure A Class 2B Standard Solution (Water-Soluble)

■ Analysis of a Sample (Water-Soluble Sample)

Fig. 5 shows chromatograms for a standard solution and pharmaceutical test solution. Although peak a eluted with almost the same retention time as cumene in the FID chromatogram and was estimated to be cumene (Fig. 6), checking the mass spectrum of peak a revealed it to be α-pinene (Fig. 7).

Misidentification errors like this can be prevented by using GC-MS to check mass spectra.

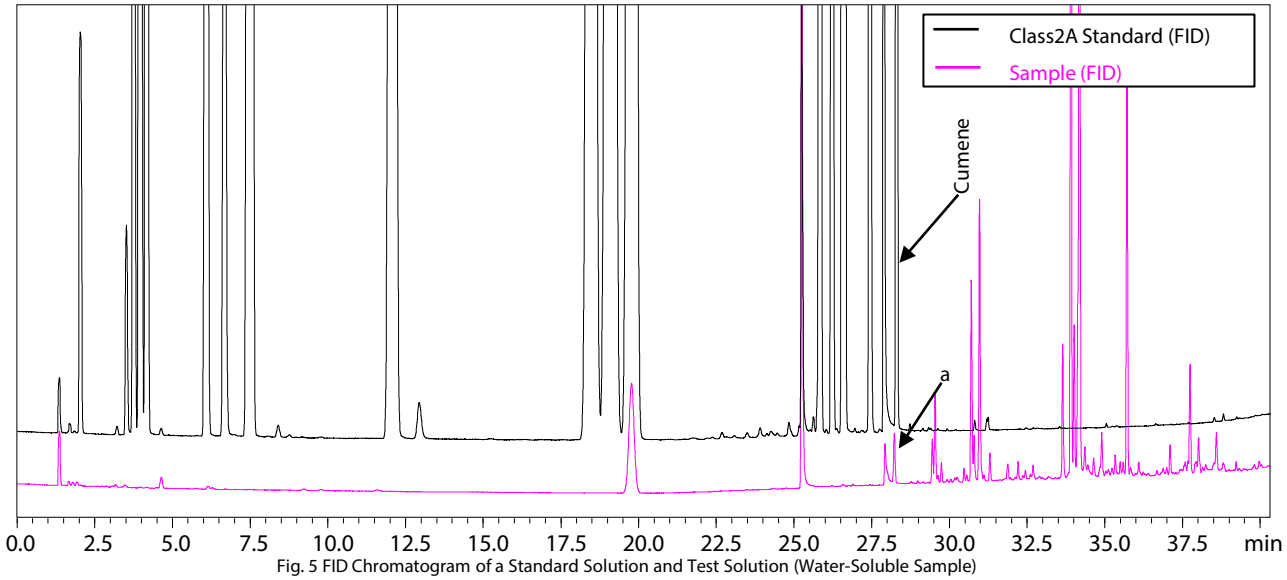

Fig. 5 FID Chromatogram of a Standard Solution and Test Solution (Water-Soluble Sample)

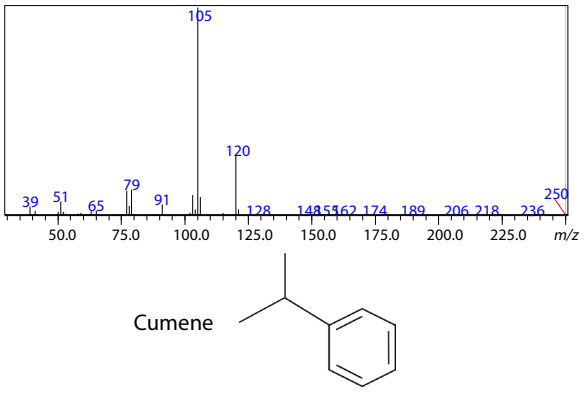

Fig. 6 Mass Spectrum of Cumene

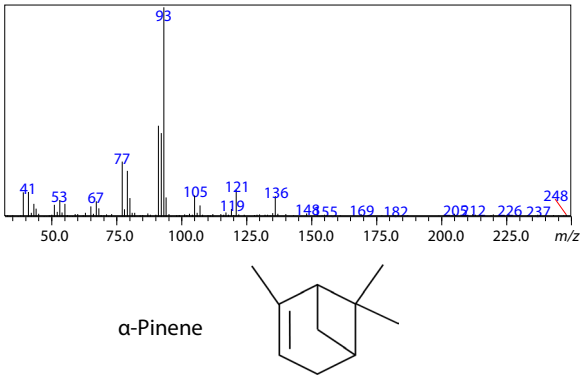

Fig. 7 Mass Spectrum of Peak a

■ Using LabSolutions GCMS for Analysis

The GCMS-QP2020 NX was controlled using LabSolutions integrated analysis software. An example analysis window is shown in Fig. 8. The software uses graphical icons for more intuitive control.

The software can be used to control both GC-FID analysis and GC-MS analysis. LabSolutions DB/CS also provides support for data integrity to prevent data falsification, data replacement, and other issues.

Fig. 8 Analysis Window from LabSolutions™ GCMS

■ Conclusion

Tests for residual solvents in pharmaceuticals were performed using HS-GC/MS and HS-GC. Good separation was obtained for t-BuOH and CPME, both of which were recently recommended for classification as Class 2 solvents in ICH Q3C (R8).

When analyzing a test sample, GC-MS revealed accurate qualitative information about a component that was otherwise misidentified based on FID analysis.

LabSolutions DB/CS can also be used to support data integrity.

01-00221A-EN First Edition: Sep. 2021
Revision A: Oct.2022

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