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

Application News

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

Y. Nagao, A. Hashimoto, A. Miyamoto

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 United States Pharmacopeia General Chapter <467> Residual Solvents describes 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-insoluble 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 Procedure A for water-insoluble samples in USP<467>. Note that solvent solutions were diluted with DMF. 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-insoluble samples based on 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-Insoluble 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 for each compound in a Class 1 standard solution.

These results meet the acceptance criterion for Procedure A system suitability testing: an S/N ratio of 1,1,1-trichloroethane of not less than 5.

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

Peak No.	Compound	S/N Ratio*1 (n=6)
1	1,1-Dichloroethane	152
2	1,1,1-Trichloroethane	148
3	Carbon tetrachloride	12
4	Benzene	104
5	1,2-Dichloroethane	36

*1 The S/N ratio is for reference purposes and not intended to be guaranteed values.

■ Analysis of Standard Solutions (Water-Insoluble Samples)

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.

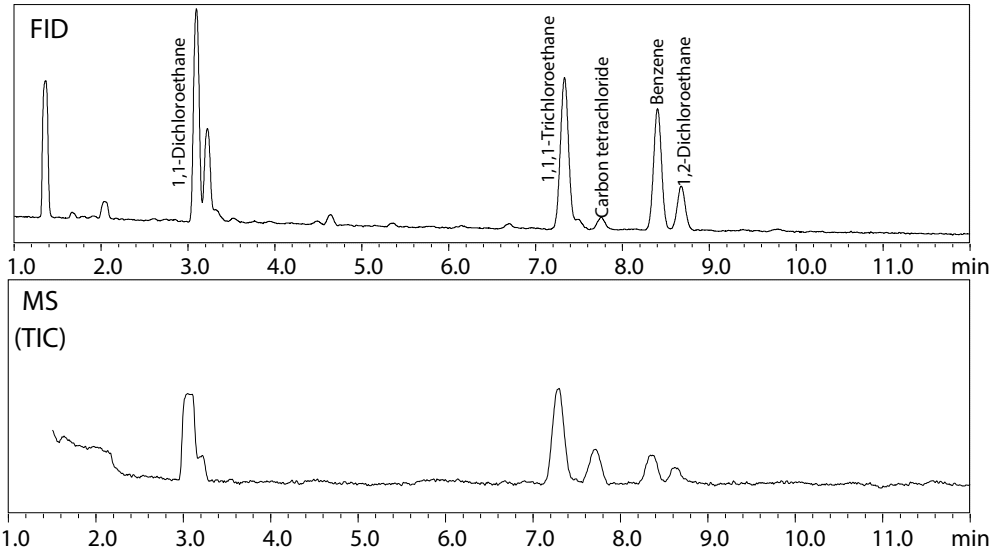

Fig. 2 Chromatogram of Procedure A Class 1 Standard Solution (Water-Insoluble)

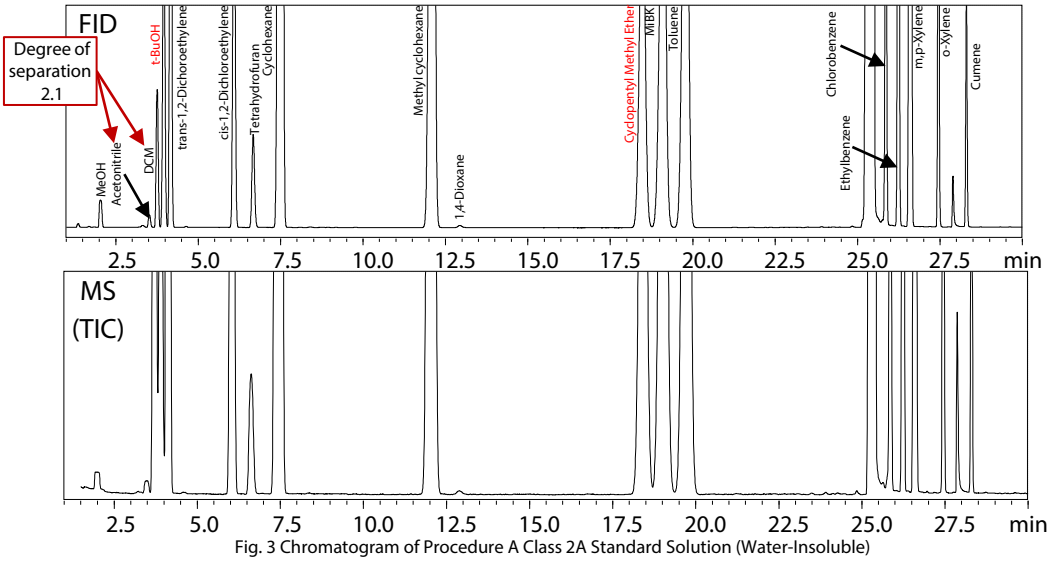

Fig. 3 Chromatogram of Procedure A Class 2A Standard Solution (Water-Insoluble)

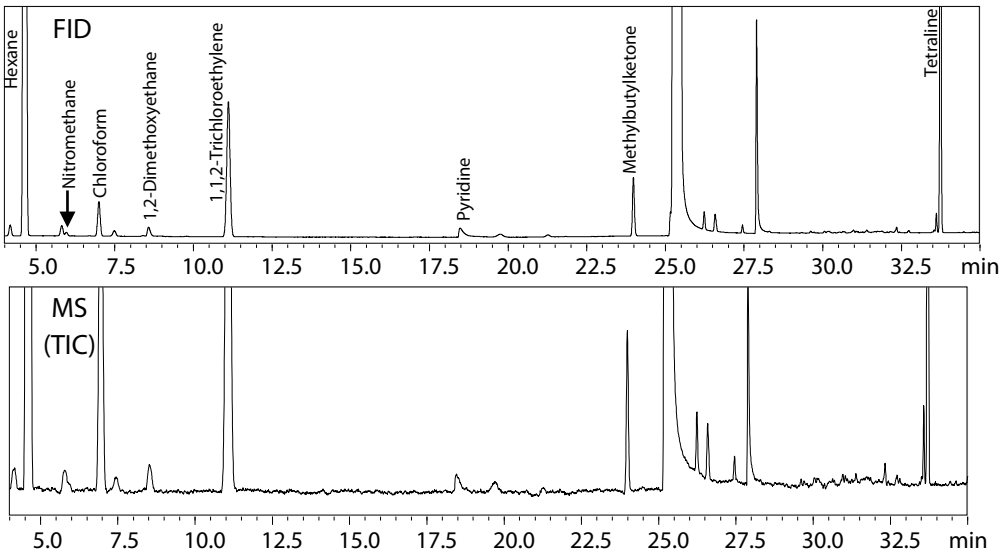

Fig. 4 Chromatogram of Procedure A Class 2B Standard Solution (Water-Insoluble)

■ Sample Analysis (Water-Insoluble Sample)

Fig. 5 shows the TIC chromatogram for a pharmaceutical analyzed as a test solution. FID analysis showed that there were no residual solvents with results equivalent to the reference standard but several other unknown peaks were detected. Analyzing unknown peaks a, b, and c by MS revealed them to be L-menthone, menthol, and menthyl acetate, in that order (Fig. 6 to 8).

GC-MS allows for qualitative analysis of unknown components detected during residual solvent testing that are not targeted solvents. Safer and more rigorous quality control can be achieved by using mass spectrometry to identify components that are otherwise difficult to distinguish based on FID analysis.

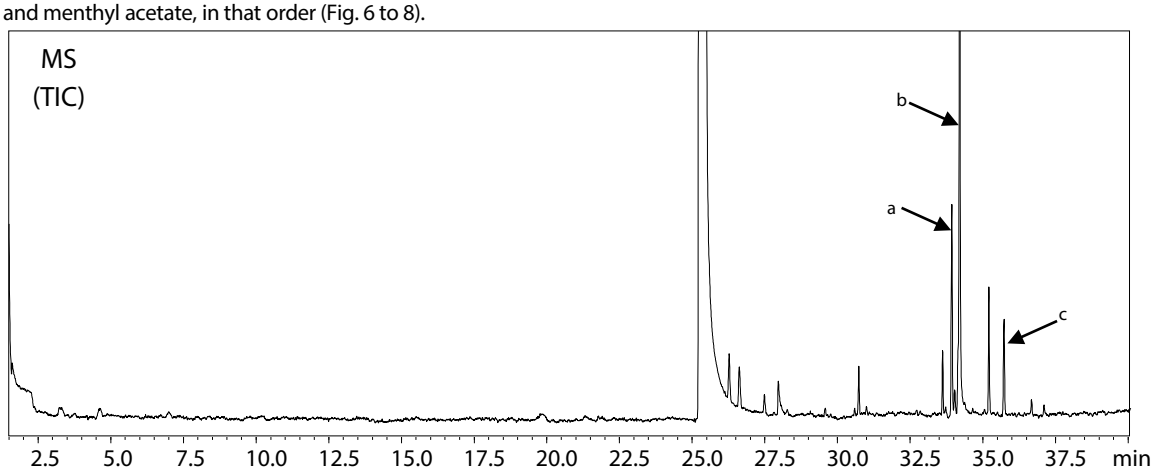

Fig. 5 TIC Chromatogram of Test Solution (Water-Insoluble Sample)

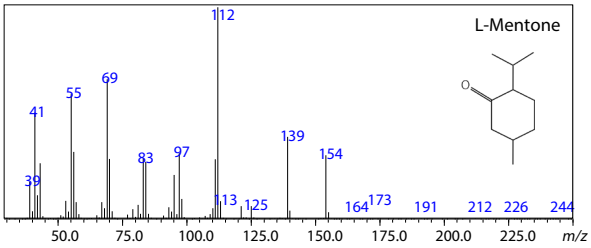

Fig. 6 Mass Spectrum of Peak a

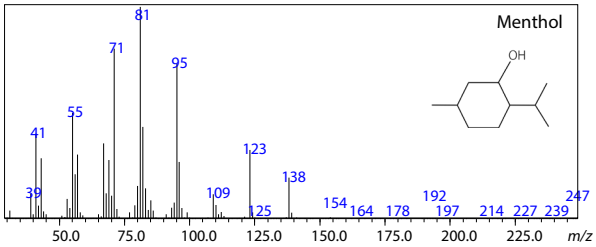

Fig. 7 Mass Spectrum of Peak b

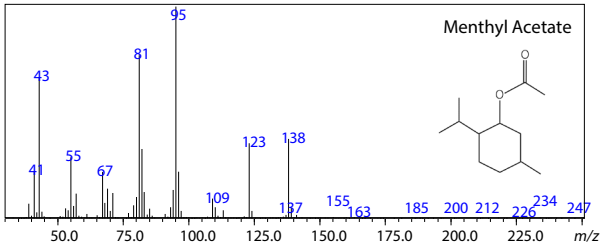

Fig. 8 Mass Spectrum of Peak c

■ Using LabSolutions GCMS for Analysis

The GCMS-QP2020 NX was controlled using LabSolutions integrated analysis software. An example analysis window is shown in Fig. 9. 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.

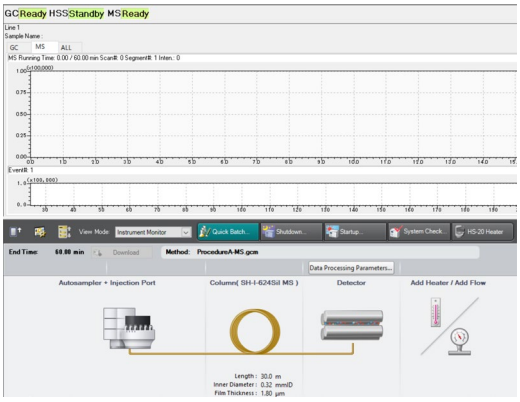

Fig. 9 Analysis Window from LabSolutions™ GCMS

■ 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 qualitative information about unknown components detected during residual solvent testing that were not targeted solvents and that were difficult to distinguish based on FID analysis.

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

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