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Application News

No. G303A

Gas Chromatography

Analysis of Residual Solvents in Pharmaceuticals An Analysis Method for Class 2 Solvents (Water-Soluble Samples) Unsuited to Headspace GC Methods

Testing methods for residual solvents in pharmaceuticals are defined in the Japanese Pharmacopoeia Seventeenth Edition and USP (U.S. Pharmacopeia), General Chapters <467> Residual Solvents. While these testing methods mainly describe the detailed testing procedures for Class 1 and Class 2 residual solvents using headspace GC methods, there is no mention of testing methods for solvents possibly used in the testing of compounds and water-insoluble pharmaceuticals, which are unsuited to headspace analysis.

This article presents an analysis and examination of the water-soluble samples listed in Table 1, "Solvents Possibly Used in the Testing of Compounds and Water-Insoluble Pharmaceuticals Unsuited to Headspace Analysis (Class 2C)."

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Sample and Standard Solution Preparation

When preparing the water-soluble samples, each sample was diluted by a factor of 50 with distilled water and was centrifuged at 3,000 rpm for three minutes, and the supernatant was injected into a gas chromatograph (Fig. 1). *

A Class 2C standard solution was prepared by mixing and diluting the compounds listed in Table 1 to the concentrations equivalent to the limits.

Table 1 Solvents Possibly Used in the Testing of Compounds and Water-Insoluble Pharmaceuticals Unsuited to Headspace Analysis (Class 2C)

	Compounds	Concentration limit (ppm)	Limit equivalent concentration (µg/mL) *1
1	2-Methoxyethanol	50	1.0
2	2-Ethoxyethanol	160	3.2
3	N,N-Dimethylformamide	880	17.6
4	N,N-Dimethylacetamide	1090	21.8
5	Ethyleneglycol	620	12.4
6	N-Methylpyrrolidone	530	10.6
7	Formamide	220	4.4
8	Sulfolane	160	3.2

*1 The limit equivalent concentration when the sample is diluted by a factor of 50.

Instrument Configuration and Analysis Conditions

Table 2 lists the analysis conditions. The Class 2C standard solution and sample solution (headache medication) were measured with the Nexis™ GC-2030 gas chromatograph using the direct liquid injection method. To ensure a 1:1 split ratio during injection, measurement was performed in the high pressure injection mode with the injection pressure at 48 kPa and a hold time of 0.5 minutes.

Table 2 Analysis Conditions

Model	: Nexis™ GC-2030 + AOC-20i Plus
Detector	: FID-2030 flame ionization detector
Injector temperature	: 160 °C
Column	: SH-PolarWax (0.53 mm × 30 m, d.f. = 1 µm) *1
Column temperature	: 50 °C (7 min) – 4 °C/min – 110 °C (0 min) - 10 °C/min – 220 °C (20 min *2) Total: 53 min
High press injection	: High pressure injection, automatic (48 kPa, 0.5 min)
Carrier gas controller	: Pressure mode (He)
Pressure	: 26.6 kPa (during analysis)
Injection mode	: Split 1:1 (0.5 min) (during injection)
Total flow	: 23 mL/min
Linear velocity	: 37.0 cm/sec (26.6 kPa, 50 °C)
Column flow	: 5.1 mL/min (26.6 kPa, 50 °C)
Purge flow	: 3 mL/min
Detector temperature	: 240 °C
Detector gas	: H_2 32.0 mL/min, Air 200 mL/min
Makeup gas	: He 24 mL/min
Injection volume	: 1 µL
Syringe	: Elastic syringe, AOC (P/N: 221-49548)

*1 P/N: 221-75979-30

*2 Since the sample solution may contain high boiling point components, it is recommended to set a long hold time at 220 °C.

This analysis was performed using 30 mg of deactivated glass wool (P/N: 221-48600) packed into the glass insert for splitting (P/N: 221-41444-84). It is possible to perform analysis with favorable repeatability by filling the glass insert with about three times the normal amount of wool.

* The occurrence of interference peaks can be reduced by removing insoluble components from the solvents.
If the solvents do not contain any insoluble components, centrifugal separation can be skipped.

Analysis of Class 2C Standard Solution

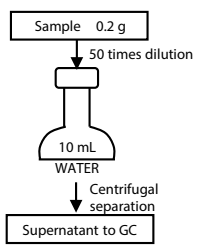

Fig. 1 Sample Solution Preparation

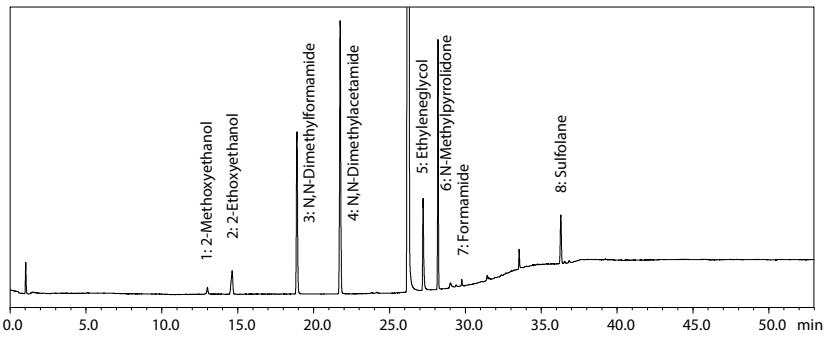

Fig. 2 Chromatogram of Class 2C Standard Solution at Limit Equivalent Concentration

Comparison of Class 2C Standard Solution and Class 2A and 2B Standard Solution

Class 2A and 2B standard solutions were analyzed under the same analysis conditions and compared to the chromatogram of the Class 2C standard solution. The separation of components were verified.

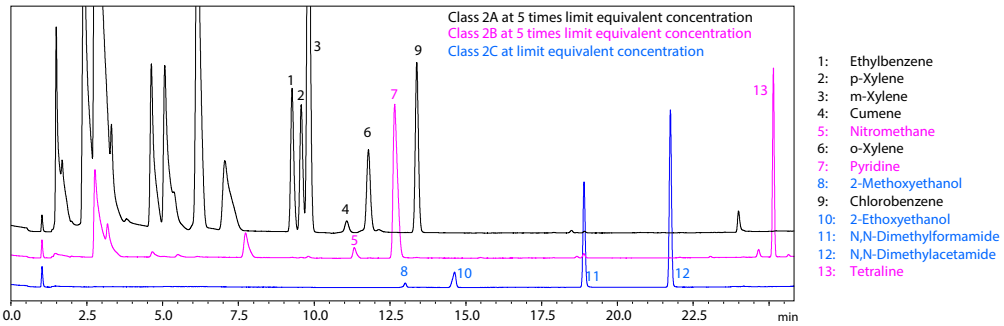

Fig. 3 Superimposed Chromatograms of Class 2C Standard Solution and Class 2A and 2B Standard Solutions

Repeatability of Class 2C Standard Solution

Table 3 Repeatability of Area Values of Class 2C Standard Solution at Limit Equivalent Concentration (n = 6)

	2-Methoxyethanol	2-Ethoxyethanol	N,N-Dimethylformamide	N,N-Dimethylacetamide	Ethyleneglycol	N-Methylpyrrolidone	Formamide	Sulfolane
1	1,882	9,983	45,204	76,264	23,521	45,031	1,252	12,876
2	1,910	9,940	45,176	76,567	21,876	45,151	1,193	12,930
3	1,799	9,895	44,644	75,300	22,151	44,319	1,178	12,740
4	1,829	9,870	44,523	75,304	22,788	44,483	1,289	12,917
5	1,759	9,747	43,900	73,858	22,478	43,824	1,222	12,669
6	1,741	9,693	43,916	74,185	22,390	43,797	1,217	12,646
Average	1,820	9,855	44,560	75,246	22,534	44,434	1,225	12,796
%RSD	3.68	1.14	1.29	1.44	2.54	1.30	3.29	0.99

Analysis of Sample Solution

A sample of headache medication solution and a sample spiked with limit equivalent concentration standard were centrifuged, and the supernatant was analyzed.

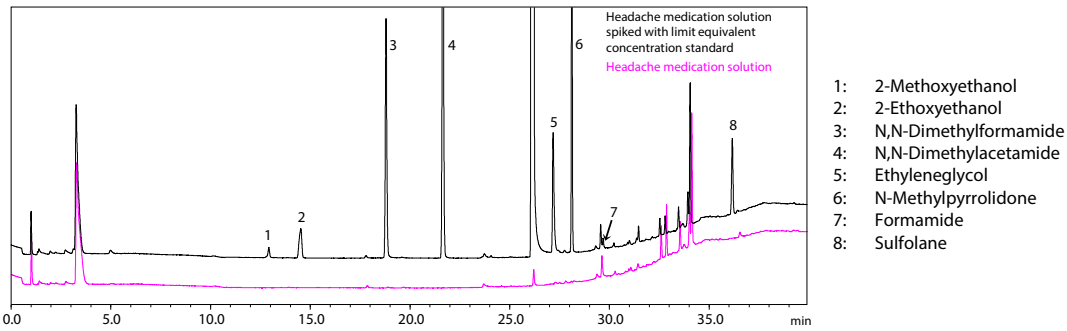

Fig. 4 Chromatograms of Samples of Headache Medication Solution and Spiked with Limit Equivalent Concentration Standard

Average Recovery Rate and Repeatability of Sample Solution

The sample of headache medication solution spiked with limit equivalent concentration standard was analyzed six times consecutively. Table 4 shows the average recovery rate (%) and the repeatability (n = 6) of the recovery rate (quantitation value / limit equivalent concentration × 100). The average recovery rate was favorable between 91 % and 107 % and the repeatability was also favorable at less than 4 % for all compounds.

Table 4 Average Recovery Rate and Repeatability of Sample Solution (n = 6)

Compounds	Average Recovery Rate (%)	Recovery Rate Repeatability (%RSD)
2-Methoxyethanol	100	2.58
2-Ethoxyethanol	103	0.48
N,N-Dimethylformamide	103	0.45
N,N-Dimethylacetamide	104	0.29
Ethyleneglycol	107	1.68
N-Methylpyrrolidone	104	0.46
Formamide	91	4.00
Sulfolane	104	0.76

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