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Application Data Sheet No.1	GC Gas Chromatograph Measurement of Residual Solvents in Pharmaceuticals by Headspace GC - USP <467> Residual Solvents - Procedure A -

Residual solvents in pharmaceuticals are defined as volatile organic compounds used in or generated from the manufacture of drug substances, pharmaceutical additives, or drug products. They are strictly controlled according to risk classifications from Class 1 to Class 3, which are based on the risk to human health.

Headspace GC methods specified in the USP (U.S. Pharmacopeia), General Chapters <467> Residual Solvents, are commonly used for analysis of residual solvents. These USP methods were created based on the analytical methods specified in the EP (European Pharmacopoeia), in accordance with policies specified by the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

This Application Data Sheet presents data obtained using the Shimadzu HS-20 Headspace Sampler and Shimadzu GC-2010 Plus Gas Chromatograph, from Class 1 and Class 2 standard solutions, in accordance with Water-Soluble Articles, Procedure A, in USP <467> Residual Solvents.

Analysis Conditions

HS-20

Oven Temp.:	80 °C	Shaking Level:	Off
Equilibrating Time:	60 min	Sample Pressurization:	75 kPa
Pressurizing Time:	1 min	Load Time:	0.5 min
Injection Time:	1 min	Needle Flush Time:	20 min
Sample Line Temp.:	110 °C	Transfer Line Temp.:	120 °C
Vial Capacity:	20 mL		

GC-2010 Plus

Column:	Rxi-624SilMS 032 mm × 30 m, d.f. = 1.8 um	Split Ratio: Hydrogen:	1:5 40 mL/min
Column Temp.:	40 °C (20 min) – 10 °C/min – 240 °C (20 min)	Air:	400 mL/min
Carrier Gas Linear Velocity:	35 cm/sec (helium)		
FID Temp.:	260 °C		
Makeup Gas:	30 mL/min (helium)		

Results

1. Class 1

Figure 1 shows the Class 1 standard solution chromatogram. Procedure A requires that the S/N ratio obtained for 1,1,1-Trichloroethane in this chromatogram be 5 or higher. As shown, the S/N ratio was 200. Even for carbon tetrachloride, which had the lowest sensitivity level, the S/N was 10.
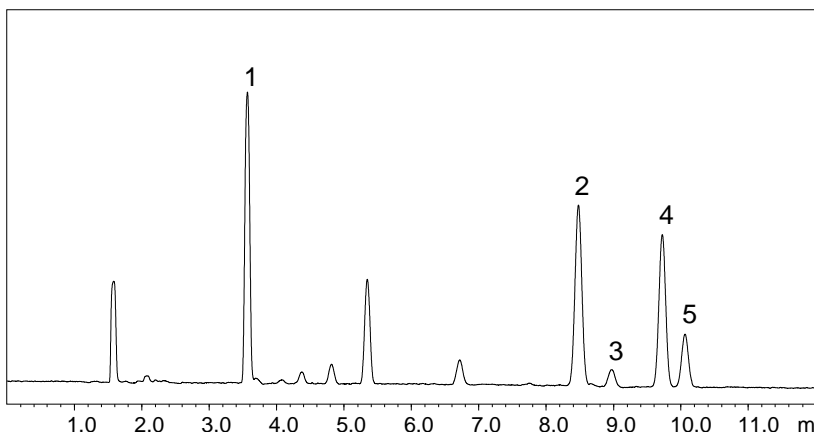

		S/N Ratio
1	1,1-Dichloroethene	330
2	1,1,1-Trichloroethane	200
3	Carbontetrachloride	10
4	Benzene	170
5	1,2-Dichloroethane	50

Fig. 1: Water-Soluble Articles, Procedure A, Class 1 Standard Solution Chromatogram

2. Class 2
Due to the large number of components in the Class 2 standard solution, it was separated into two mixtures: A and B. Respective measurement results are shown in Figures 2 and 3.
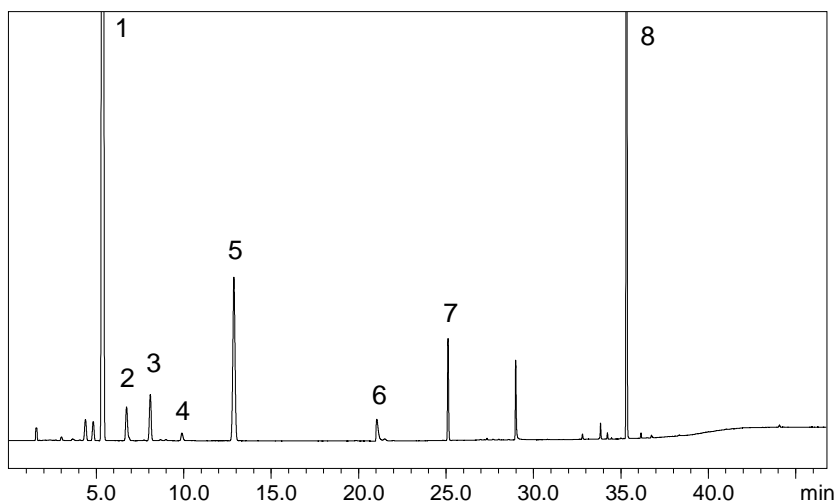
Class 2 Mixture A
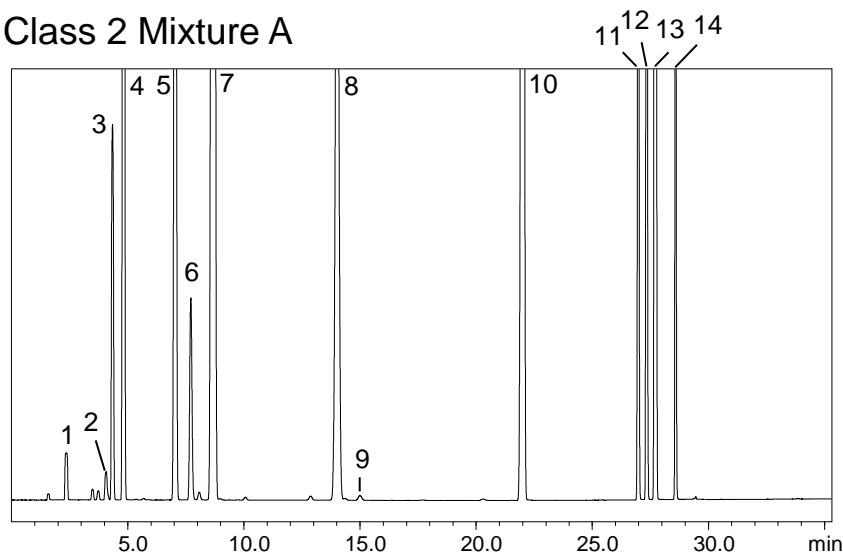
1 Methanol
2 Acetonitrile
3 Methylene chloride
4 trans-1,2-Dichloroethene
5 cis-1,2-Dichloroethene
6 Tetrahydrofran
7 Cyclohexane
8 Methylcyclohexane
9 1,4-Dioxane
10 Toluene
11 Chlorobenzene
12 Ethylbenzene
13 m+p-Xylene
14 o-Xylene

Fig. 2: Water-Soluble Articles, Procedure A, Class 2 Mixture A Standard Solution Chromatogram

Class 2 Mixture B

1 Hexane
2 Nitromethane
3 Chloroform
4 1,2-Dimethoxyethane
5 Trichloroethene
6 Pyridine
7 Methylbutylketone
8 Tetraline

Fig. 3: Water-Soluble Articles, Procedure A, Class 2 Mixture B Standard Solution Chromatogram

Procedure A requires that the resolution for acetonitrile and methylene chloride in the Class 2 standard solution Mixture A chromatogram be 1.0 or greater. Figure 4 shows that, using the Restek Rxi-624SilMS low-bleed column, the specified peaks are completely separated, with a resolution of 1.5.
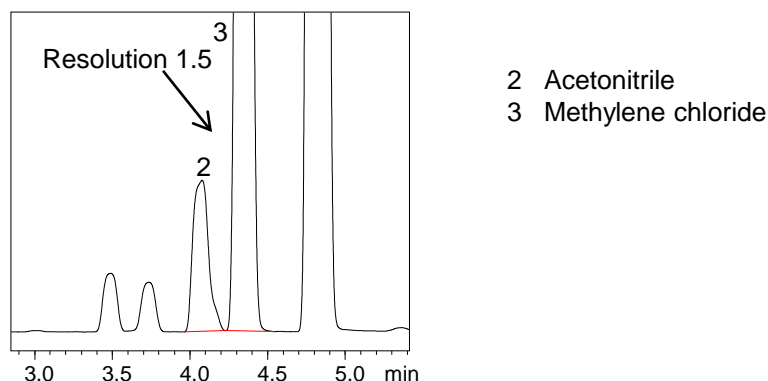

2   Acetonitrile
3   Methylene chloride

Fig.4: Separation Between Acetonitrile and Methylene Chloride

The area repeatability (RSD %) was evaluated by measuring the sample 20 consecutive times. The resulting RSD % value was between 1 % and 3 %, which indicates a higher repeatability than obtained using previous headspace samplers (see Table 1).

The HS-20 headspace sampler achieves this unprecedented high repeatability by maintaining a uniform temperature distribution within the air tank oven and by using an advanced pressure control (APC) system for precise pressure control.

	RSD % n=20
Class 2A	
2 Acetonitrile	1.1
3 Methylene chloride	1.7
4 trans-1,2-Dichloroethene	2.3
5 cis-1,2-Dichloroethene	1.9
6 Tetrahydrofuran	0.6
10 Toluene	2.5
11 Chlorobenzene	2.5
Class 2B	
4 1,2-Dimethoxyethane	3.1
6 Pyridine	2.6

Table 1:Peak Area Repeatability of Class 2A & 2B

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