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Application Data Sheet

No.2

GC
Gas Chromatograph

Measurement of Residual Solvents in Pharmaceuticals by Headspace GC - USP <467> Residual Solvents - Procedure B -

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 B, 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		

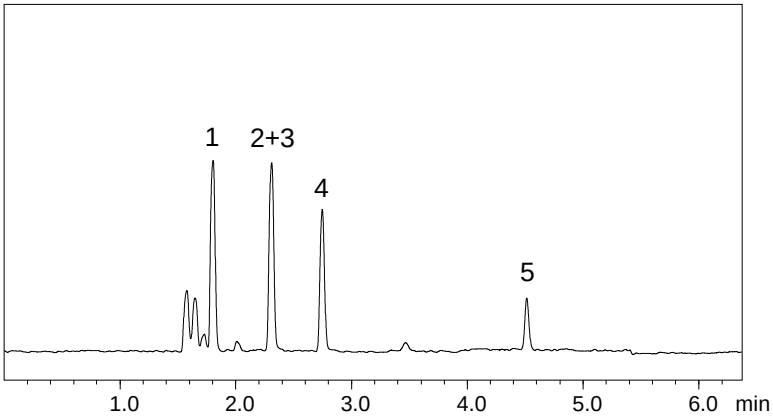
GC-2010 Plus

Column:	StabilWAX 032 mm × 30 m, d.f. = 0.25 um	Split Ratio:	1:10
		Hydrogen:	40 mL/min
Column Temperature:	50 °C (20 min) – 6 °C/min – 165 °C (20 min)	Air:	400 mL/min
Carrier Gas Linear Velocity:	35 cm/sec (helium)		
FID Temperature:	250 °C		
Makeup Gas:	30 mL/min (helium)		

Results

1. Class 1

Figure 1 shows the Class 1 standard solution chromatogram. Procedure B requires that the S/N ratio obtained for benzene in this chromatogram be 5 or higher. In this example, the S/N ratio for benzene was 60.

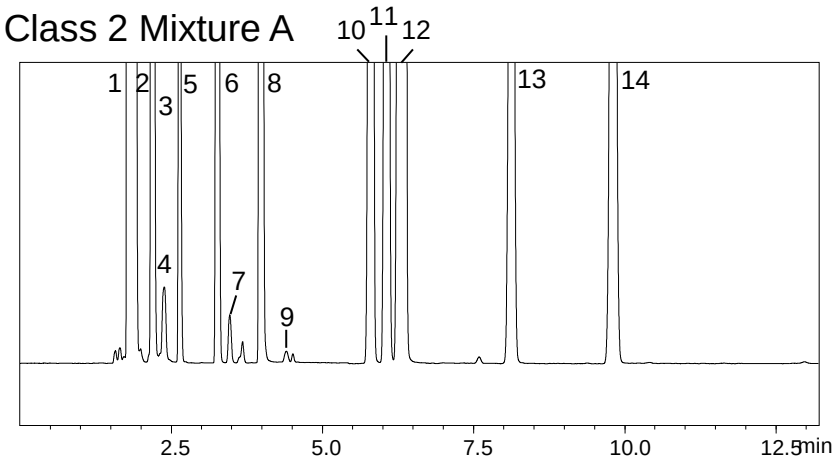


		S/N Ratio
1	1,1-Dichloroethene	80
2	1,1,1-Trichloroethane	80
3	Carbontetrachloride	-
4	Benzene	60
5	1,2-Dichloroethane	20

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

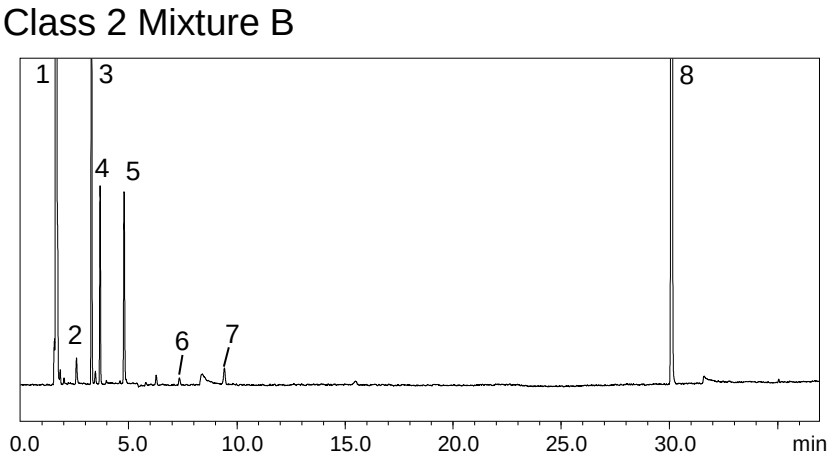
2. Class 2

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.



1 Cyclohexane
2 Methylcyclohexane
3 trans-1,2-Dichloroethene＋Tetrahydrofran
4 Methanol
5 Methylene chloride
6 cis-1,2-Dichloroethene
7 Acetonitrile
8 Toluene
9 1,4-Dioxane
10 Ethylbenzene
11 p-Xylene
12 m-Xylene
13 o-Xylene
14 Chlorobenzene

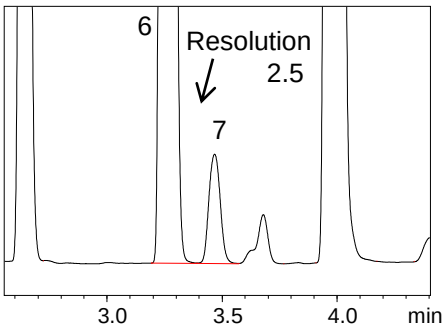
Fig. 2: Water-Soluble Articles, Procedure B, Class 2 Mixture A Standard Solution Chromatogram



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

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

Procedure B requires that the resolution for cis-1,2-dichloroethene and acetonitrile in the chromatogram measured from the Class 2 standard solution Mixture A be 1.0 or greater. Figure 4 shows that, using the Restek StabilWAX column, the specified peaks are completely separated, with a resolution of 2.5.



6 cis-1,2-Dichloroethene
7 Acetonitrile

Fig. 4: Separation Between cis-1,2-Dichloroethene and Acetonitrile

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