Application Note: ANCCSRESSOLV 1010

Analysis of Residual Solvents using GC/FID with Headspace and a Cyanopropylphenyl Polysiloxane Phase

A. Khan, L. Pereira, Thermo Fisher Scientific, Runcorn, Cheshire, UK

Key Words

- TRACE TR-V1 Column
- Residual Solvents in Pharmaceutical Products
- USP 467 method

Overview

A Thermo Scientific TRACE Ultra GC system with a Thermo Scientific TriPlus Autosampler was used for the analysis of residual solvents in accordance with USP method 467.[1] The column used for the analysis was a Thermo Scientific TRACE TR-V1 column.

Introduction

This application note describes the analysis of residual solvents according to the revised (effective July 2007) US Pharmacopeia (USP) method. The method is used for analyzing trace levels of solvents that are involved in the production of a drug, excipient or product packaging in the pharmaceutical industry. Drug products should contain low levels of residual solvents as determined by safety data.

The USP 467 method involves the analysis of 53 solvents grouped according to their genotoxic hazards:

- **Class 1 solvents** (known to cause unacceptable toxicities) should be avoided in the manufacturing process.
- **Class 2 solvents** (associated with less severe toxicity) should be limited.
- **Class 3 solvents** (less toxic) should be used where practical.

Three analytical procedures are used for identification and quantification of the residual solvents:

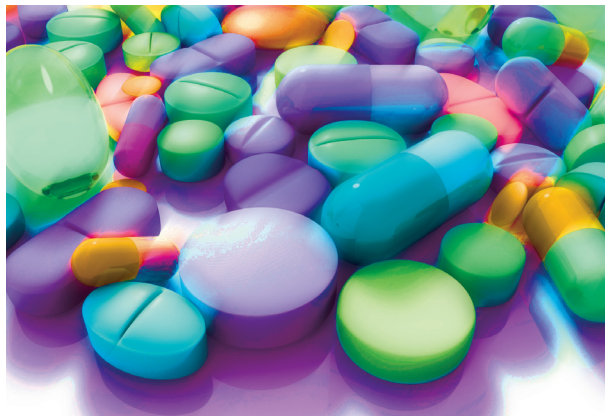
- **Procedure A** is used for screening and confirmation of the solvents identity and use a G43 (volatiles) column.
- **Procedure B** is used for confirmation of the solvents identity using a G16 (wax) column.
- **Procedure C**, which uses a G43 column, is required to quantify the amount of residual solvents.

Methods

Samples

USP 467 test mixtures solutions prepared according to USP 467 method

Column	Part Number
TRACE™ TR-V1 30 m × 0.32 mm × 1.8 µm	260V339P



GC/FID Conditions

TriPlus Headspace Autosampler

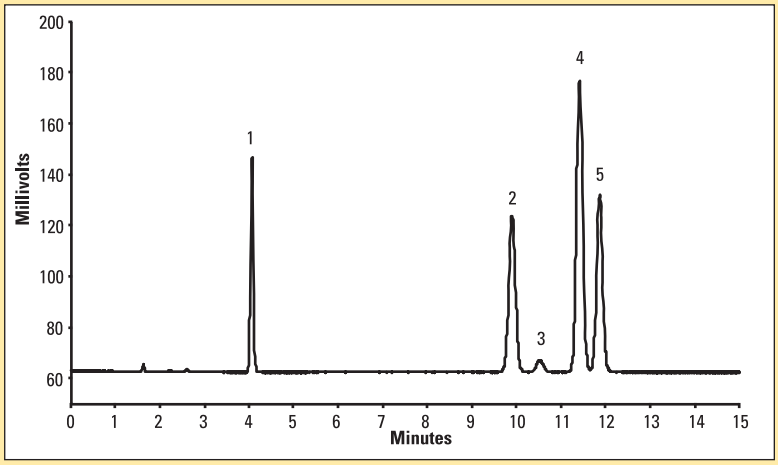
Sample Volume	1 mL
Sample Analysis Time	30 min
Agitator Temperature	80 °C
Incubation Time	45 min
Agitator Shake	On 10 s, Off 20 s
Syringe Temperature	100 °C
Post Injection Flush	30 s

TRACE GC Ultra

Oven Program	40 °C (20 min), 10 °C/min, 240 °C (10 min)
Equilibration Time	0.5 min.
Injector	140 °C
Split Flow	40 mL/min
Column Flow	2.0 mL/min (constant)
Detector	FID at 240 °C
Detector Air Flow	350 mL/min
Detector H_2 Flow	35 mL/min
Detector N_2 Makeup Flow	30 mL/min

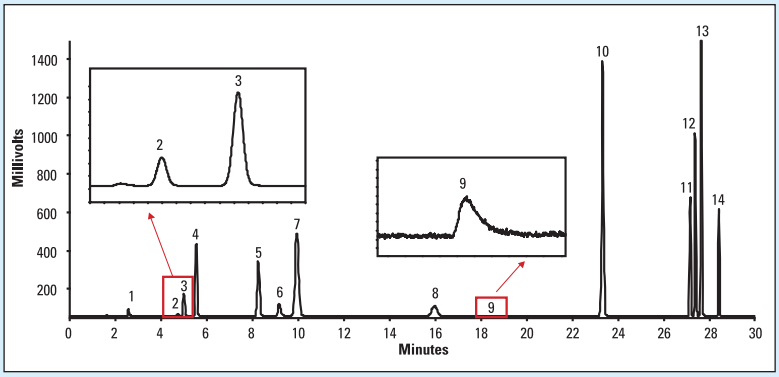
Consumables	Part Number
TR-Green septa	313G3211
Thermo Scientific Split FocusLiner for 50 mm needle with Quartz Wool	453T1905
Liner graphite seal	29033406
Graphite ferrule for 0.32 mm ID column	29013487
2.5 mL headspace syringe	36503006
20 mL clear crimp top vial	60180-506
Aluminum 20 mm cap and Si/PTFE seal	60180-511

Thermo SCIENTIFIC



Peak #	Peak Identification	Rt (min)	Measured S/N	Specified S/N
1	1,1-Dichloroethane	4.06	108	> 3
2	1,1,1-Trichloroethane	9.90	186	> 5
3	Carbon Tetrachloride	10.53	15	> 3
4	Benzene	11.43	351	> 3
5	1,2-Dichloroethane	11.87	213	> 3

Figure 1: GC/FID chromatogram for class 1 residual solvents



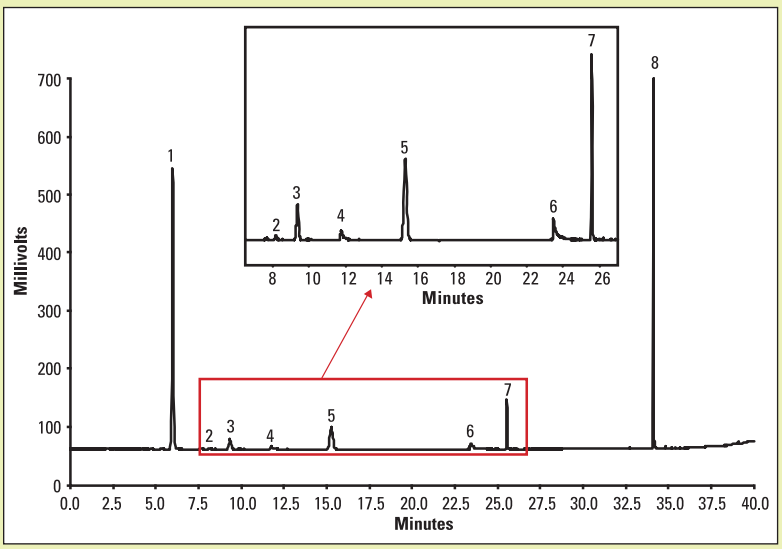
Peak #	Peak Identification	Rt (min)
1	Methanol	2.58
2	Acetonitrile	4.71
3	Dichloromethane	5.00
4	*Trans*-1,2-Dichloroethane	5.53
5	*Cis*-1,2-Dichloroethane	8.25
6	Tetrahydrofuran	9.16
7	Cyclohexane	9.94
8	Methylcyclohexane	15.97
9	1,4-Dioxane	18.35
10	Toluene	23.33
11	Chlorobenzene	27.17
12	Ethyl Benzene	27.39
13	m-Xylene/p-Xylene	27.64
14	o-Xylene	28.42

Figure 2: GC/FID chromatogram for class 2A residual solvents

Results and Discussion

The acceptance criteria for USP 467, class 1 solvents, is that the signal-to-noise ratio for 1,1,1-Trichloroethane (peak 2) is greater than 5 and that the signal-to-noise ratio obtained from the other compounds in the class is greater than 3. The chromatogram and signal to noise measurements obtained using the method described previously are shown in Figure 1.

The USP 467 method specification for class 2 solvents is that the resolution between acetonitrile and dichloromethane (peaks 2 and 3) is not less than 1.0. The chromatograms obtained for class 2 solvents (mixture A and mixture B) are shown in Figures 2 and 3. The method criteria for resolution between the critical pair is met as these are fully resolved. All the other components are also fully resolved, which demonstrates good selectivity and efficiency of the chromatographic separation taking place in the TRACE TR-V1 column. Poor response was observed for 1,4-Dioxane, which was expected.



Peak #	Peak Identification	Rt (min)
1	Hexane	6.00
2	Nitromethane	8.17
3	Chloroform	9.36
4	1,2-Dimethoxyethane	11.78
5	Trichloroethylene	15.30
6	Pyridine	23.45
7	2-Hexanone	25.57
8	Tetralin	34.15

Figure 3: GC/FID chromatogram for class 2B residual solvents

Conclusions

The criteria set by the USP 467 method is met, therefore the TRACE GC Ultra with headspace configuration and TRACE TR-V1 column provides excellent capability to run the residual solvent method, screening procedure.

The signal-to-noise specifications set in USP 467 for Class 1 residual solvents were easily exceeded, demonstrating that the set-up used provides a sensitive system for this analysis.

The resolution specifications set in USP 467 for Class 2 residual solvents were easily exceeded demonstrating good selectivity and efficiency of the chromatographic separation taking place in the TRACE TR-V1 column.

References

1. Residual Volatile Impurities: USP 467, 2008. USA

In addition to these offices, Thermo Fisher Scientific maintains a network of representative organizations throughout the world.

USA and Canada
+1 800 332 3331
France
+33 (0) 3 88 67 53 20
Germany
+49 6103 408 0
Switzerland
+41 56 618 41 11
United Kingdom
+44 1509 555500
Japan
+81 45 453 9220
China
800-810-5118
India
1800 22 8374 (toll-free)
+91 22 6716 2200
All Other Enquiries
+44 (0) 1928 534 050

Technical Support
North America
+1 800 332 3331
Outside North America
+44 (0) 1928 534 440

www.thermoscientific.com/chromatography

ANCCSRESSOLV 1010