Analysis of residual solvents using GC/FID with headspace and a cyanopropylphenyl polysiloxane phase

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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. The column used for the analysis was a Thermo Scientific TRACE TR-V1 column.

Introduction

This poster 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.

The method described in this poster follows procedure A and uses a cyanopropylphenyl polysiloxane phase for the analysis of volatile organic compounds, and FID detection. The analysis of Class 1 and 2 solvents is demonstrated in this work and it is shown to meet the acceptance criteria.

Methods

Samples: USP 467 test mixtures solutions prepared according to USP 467 method.

Column: TRACE™ TR-V1 30m x 0.32mm x 1.8 µm

GC/FID Conditions:

TriPlus Headspace Autosampler:
Sample Volume: 1 mL
Sample analysis time: 30 min
Agitator temperature: 80 ºC
Incubation time: 45 min
Agitator shake: On 10s, Off 20s
Syringe temperature: 100 ºC
Post injection flush: 30s

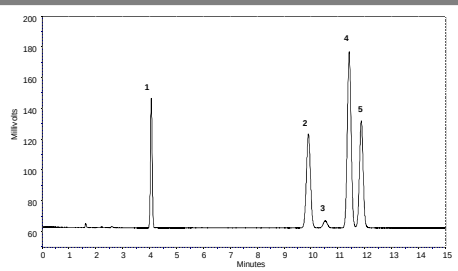
TRACE GC Ultra:
Oven Program: 40 ºC (20 min), 10 ºC/min, 240 ºC (10 min)
Equilibration time: 0.5 min.
Injector: 140 ºC
Split flow: 40 mL/min
Column Flow: 2.0 mL/min (constant)
Detector: FID at 240 ºC
Detector air flow: 350 mL/min
Detector H_2 flow: 35 mL/min
Detector N_2 makeup flow: 30mL/min

Consumables:
TR-Green Septa
Split FocusLiner™ for 50mm needle with Quartz Wool
Liner Graphite seal
Graphite ferrule for 0.32 mm i.d column
2.5mL Headspace Syringe
Graphite ferrules to fit 0.32 mm and 0.25mm ID columns
20 mL clear crimp top vial
Aluminium 20mm cap and Si/PTFE seal

Results and Discussion

The acceptance criteria for USP 467 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.

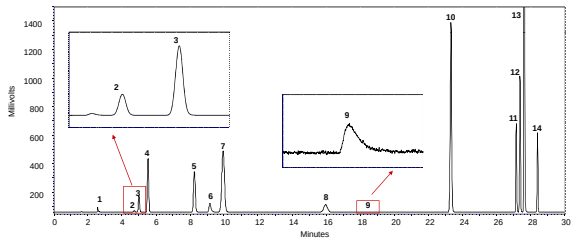
Figure 1. GC/FID chromatogram for class 1 residual solvents.



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

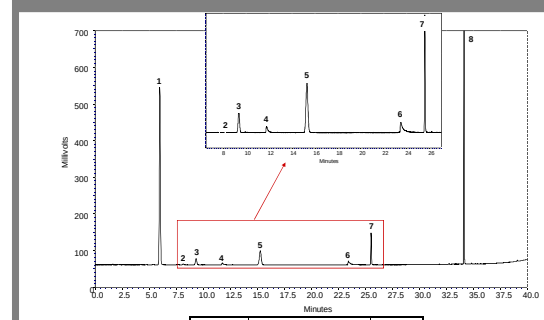
The USP 467 method specification for class 2 solvents is that the resolution between acetonitrile and dichloromethane (peaks 2 and 3) is not less than 1.0. The chromatograms obtained for class 2 solvents (mixture A and mixture B) are shown in Figures 2 and 3. The method criteria for resolution between 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.

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



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	15.3
6	Pyridine	23.45
7	2-Hexanone	25.57
8	Tetralin	34.15

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.

References

Residual Volatile Impurities: USP 467, 2008. USA

For additional information, please visit our Chromatography Resource Centre which can be found at:
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