Analysis of USP <467> Residual Solvents using the Agilent 7697A Headspace Sampler with the Agilent 7890B Gas Chromatograph

Application Note

Pharmaceuticals

Authors

Bart Tienpont, Frank David, and
Pat Sandra
Research Institute for Chromatography
Kennedypark 26
B-8500 Kortrijk
Belgium

Roger L Firor
Agilent Technologies, Inc.
2850 Centerville Rd
Wilmington, DE 19808

Abstract

USP <467> residual solvents were analyzed by static headspace on the Agilent 7697A Headspace Sampler combined with the Agilent 7890B Gas Chromatograph. The previously described method performed on an Agilent 7890A GC was directly transferred to the 7890B GC. Excellent chromatographic performance was achieved at USP <467> specified limits and equivalent results were obtained. This test clearly indicated that methods can be transferred directly from an Agilent 7890A GC to the 7890B GC without modification.

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Introduction

Residual solvent analysis is a very important quality control procedure performed in the pharmaceutical industry. Sampling is typically performed by static headspace and analysis is done by GC/FID using a dedicated column. Often, a parallel column dual channel analysis by GC/FID or GC/FID/MSD is used. Previously, different configurations were described and tested in terms of repeatability, sensitivity and resolution [1].

The described dual channel GC/FID method was evaluated on the Agilent 7890B GC. The original method was transferred to the GC, without modification. Repeatability, sensitivity, and resolution were all tested using residual solvent solutions in water of Class 1, Class 2A, and Class 2B compounds.

Experimental

Solutions

Three stock solutions of residual solvents in DMSO were used:

- Residual Solvent Revised Method 467 – Class 1 (p/n 5190-0490),

- Residual Solvent Revised Method 467 – Class 2A (p/n 5190-0492),

- Residual Solvent Revised Method 467 – Class 2B (p/n 5190-0513).

These stock solutions were diluted in water to the USP specified limits according to the following scheme:

Class 1 solvents
- 1.0 mL stock solution vial plus 9 mL DMSO diluted to 100 mL

- 1.0 mL from step 1 diluted to 100 mL with water

- 10 mL from step 2 diluted to 100 mL with water

- 1.0 mL from step 3 + 5 mL water in a 20-mL headspace (HS) vial

Class 2A solvents
- 1.0 mL stock solution vial, diluted to 100 mL

- 1.0 mL from step 1 + 5 mL water in a 20-mL HS vial

Class 2B solvents
- 1.0 mL stock solution vial, diluted to 100 mL

- 5.0 mL step 1 + 1 mL water in a 20-mL HS vial

The total sample volume was thus constant at 6 mL in 20-mL headspace vials. Assuming a 50-mg drug substance sample in the headspace vial, the final residual solvent concentrations correspond to the USP concentration limits (Table 1).

Table 1. *Residual Solvents, Peak Number, USP Concentration Limits (ppm = mg/kg) and Repeatability (n = 6) Obtained by HS-GC-FID on Column 1 (VF624)*

	Identity	USP limit (ppm)	RSD (%)
Class 1			
1	1,1-dichloroethene	8	2.3
2	1,1,1-trichloroethane	1,500	1.7
3	carbon tetrachloride	4	1.9
4	benzene	2	1.7
5	1,2-dichloroethane	5	2.1
Class 2A			
1	methanol	3,000	0.8
2	acetonitrile	410	0.8
3	dichloromethane	600	0.3
4	*trans*-1,2-dichloroethene	1,870	0.8
5	*cis*-1,2-dichloroethene	1,870	1.4
6	tetrahydrofuran	720	1.1
7	cyclohexane	3,880	1.4
8	methylcyclohexane	1,180	1.5
9	1,4-dioxane	380	1.4
10	toluene	890	1.7
11	chlorobenzene	360	0.4
12	ethylbenzene	2,170	0.6
13,14	*m*-xylene, *p*-xylene	2,170	2.2
15	*o*-xylene	2,170	2.2
Class 2B			
1	hexane	290	3.1
2	nitromethane	50	4.3
3	chloroform	60	1.7
4	1,2-dimethoxyethane	100	1.5
5	trichloroethene	80	2.0
6	pyridine	200	1.4
7	2-hexanone	50	1.6
8	tetralin	100	1.7

System Configuration

Analyses were performed on an Agilent 7697A Headspace Sampler coupled to an Agilent 7890B GC. Figure 1 shows the parallel dual column configuration.

Experimental conditions

Static headspace analysis was performed at 85 °C during 40 minutes, according to the previously described method [1]. Table 2 summarizes the experimental GC conditions. An Ultra Inert liner, p/n 5190-2295, with glass wool removed was installed in the split/spitless inlet.
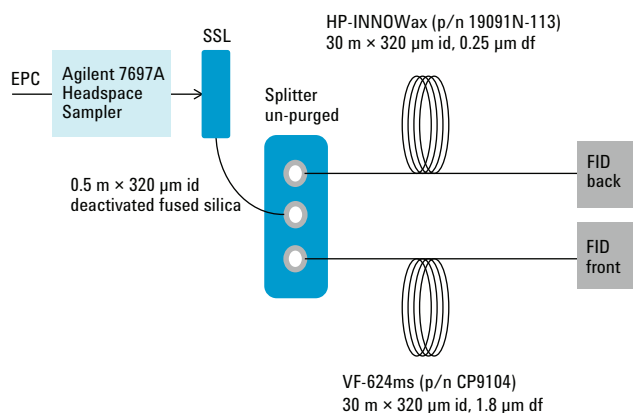

Figure1.   System configuration.

Table 2.   GC Conditions

Conditions	Agilent 7890A GC
Column A	30 m × 0.32 mm id, 1.8 µm VF-624ms (p/n CP9104)
Column B	30 m × 0.32 mm id, 0.25 µm HP-INNOWax (p/n 19091N-113)
Carrier gas	Helium, 104 kPa
Injection	Split/splitless – 140 °C – split ratio 1:5
Oven temperature	40 °C (5 minutes) to 240 °C (2 minutes) at 18 °C/min
Detection (both channels)	FID, 250 °C at 20 Hz

Results and Discussion

The chromatograms obtained for, respectively, Class 1, Class 2A, and Class 2B residual solvents are given in Figures 2–4. Peaks in the chromatograms can be identified by referring to Table 1. The obtained separations are very similar to those obtained previously on a 7890A GC [1]. Elution order, resolution, and sensitivity are equivalent.
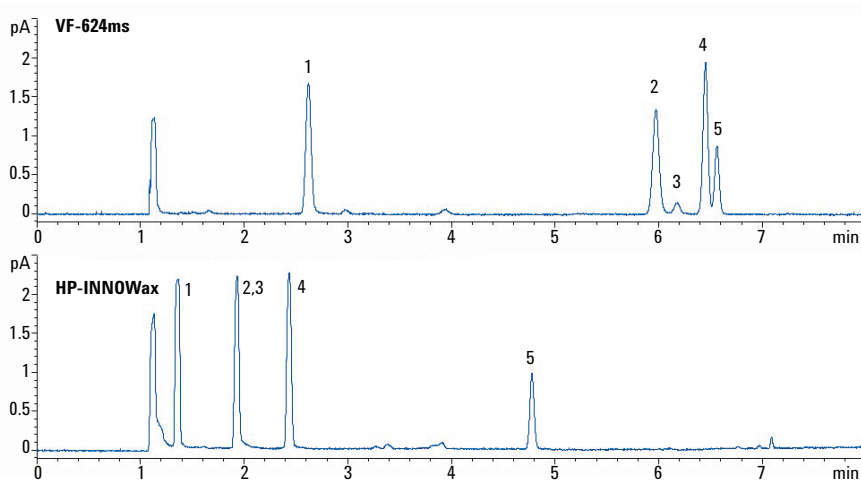

Figure 2.   Dual channel GC/FID profile of Class 1 residual solvents at USP specification limits using an Agilent 7697A Headspace Sampler and an Agilent 7890B GC (peak identification: see Table 1).
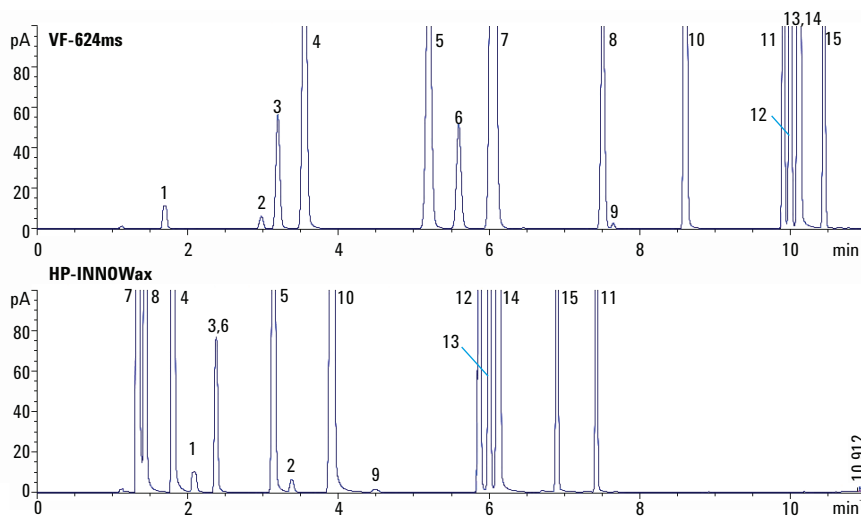
Figure 3.   Dual channel GC/FID profile of Class 2A residual solvents at USP specification limits using an Agilent 7697A Headspace Sampler and an Agilent 7890B GC (peak identification: see Table 1).

Note that Class 1 solvents benzene and 1,2-dichloroethene are baseline separated on the VF-624 column. The signal-to-noise (S/N) ratio for class 1 solvents was 18 for 1,1-dichloroethene, 31 for 1,1,1-trichloroethane, 4 for carbon tetrachloride, 42 for benzene, and 19 for 1,2-dichloroethene; all clearly better than the required S/N > 3. These values were obtained with parallel column detection (1:1 split between columns). Values using a single column would be 2x higher.

The analysis was repeated six times, and the RSDs obtained on the VF-624 column are listed in Table 1. The average RSD was 1.6%, which is excellent for static headspace sampling at these concentrations. This level of performance can be attributed to precise EPC controlled vial sampling, complete inert sample path, stable uniform thermal zones, and Capillary Flow Technology (CFT) devices.
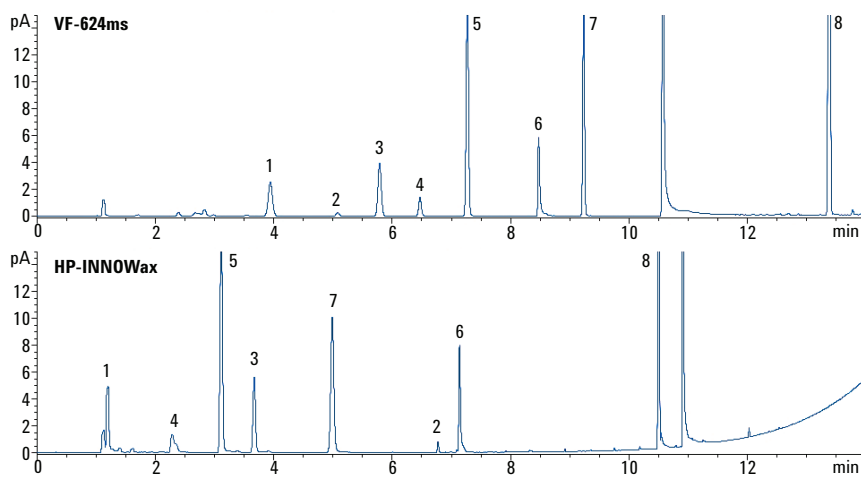

Figure 4.   Dual channel GC/FID profile of Class 2B residual solvents at USP specification limits using an Agilent 7697A Headspace Sampler and an Agilent 7890B GC (peak identification: see Table 1).

Conclusions

Methods developed for USP <467> residual solvent analysis on an Agilent 7697A Headspace sampler combined with an Agilent 7890A GC can be transferred to an Agilent 7890B GC with preserved resolution, sensitivity, and repeatability. Excellent results were obtained at USP <467> specified limit concentrations for the three classes of residual solvents.

References

1. R. L. Firor, "Analysis of USP<467> residual solvents with improved repeatability using the Agilent 7697A Headspace Sampler", Agilent Technologies application note 5990-7625EN, August 2012.

2. USP 32-NF 27, General chapter USP <467>, Organic volatile impurities, *US Pharmacopeia*, Rockville, MD, 8/2009

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