Improved Retention Time, Area Repeatability, and Sensitivity for Analysis of Residual Solvents

Application Brief

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Because many solvents pose a major risk to human health, national and international regulatory bodies such as the U.S. FDA, the United States Pharmacopoeia (USP), and the International Conference on Harmonization (ICH) require analysis for residual solvents in pharmaceutical products. Solvents are divided into three classes on the basis of possible risk. Class 1 solvents should be avoided. Class 2 solvents should be limited. Class 3 solvents are considered to have low toxic risk. The ongoing trend toward lower contaminant levels designated as safe requires more and more sensitive and accurate methods of analysis.

The system used in this study consists of an Agilent 7890A GC and an Agilent G1888 automated headspace sampler (HS). Both an EPC Aux module (HS vial pressure control) and dual mode PCM module (backpressure control of the HS vent) available on the 7890A are employed for improved headspace sampling.

Experimental

Injection port	Volatiles interface
Temperature	160 °C
Split ratio	2:1 to 4:1 typical
Carrier gas	Helium
Carrier flow	9 mL/min
7890A GC conditions	
Initial temperature	35 °C
Initial time	20 min
Rate	25 °C/min
Final temperature	250 °C
Final time	15 min
Column	30 m x 0.45 mm x 2.55 µm DB-624, Part # 124-1334
BPR set point	5.000 psig
G1888 headspace sampler	
Loop size	1 mL
Vial pressure	14 psig to 20 psig
Headspace oven	85 °C
Loop temperature	100 °C
Transfer line temperature	120 °C
GC cycle time	50 min
Pressurization	0.2 min
Vent (loop fill)	0.5 min
Inject	0.5 min

Highlights

Use of the advanced electronic pneumatics available on the 7890A result in more reliable and repeatable analysis of residual solvents by headspace-GC.

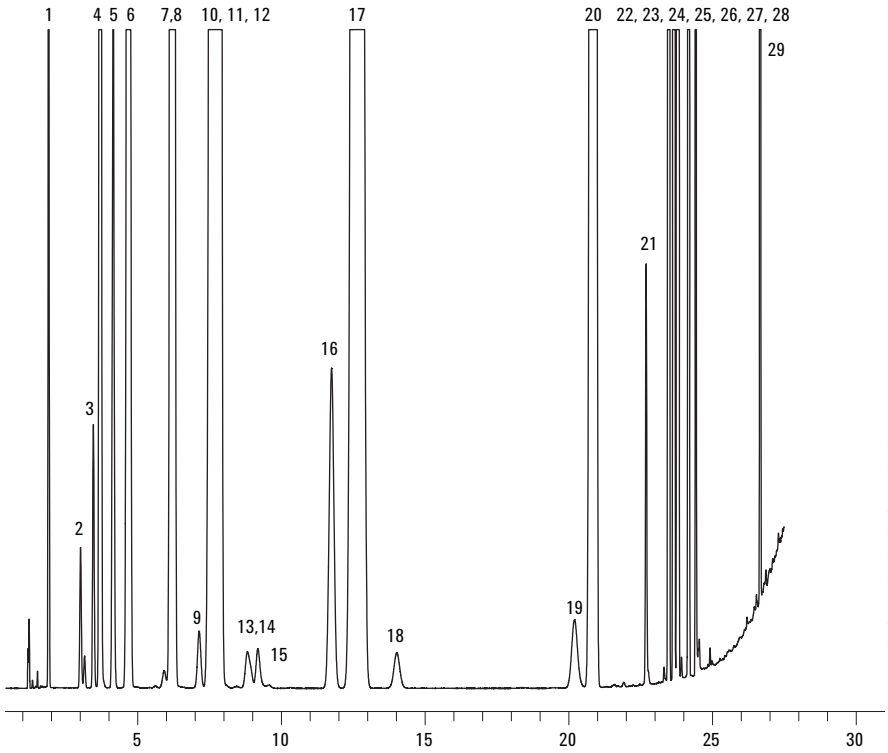
- Increased Precision: 7890A with BPR of 5.000 psi on the HS sampling loop decreased %RSD in area to 3% from 9% on an HS/6890GC system. Retention time improved to +/- 0.001 min.
- Increased Sensitivity: Pressurization of the HS loop by BPR can double the peak area vs. loop sampling at atmospheric pressure.
- Decreased Cycle Time: Backflushing of high-boiling-point solvents and late-eluting background peaks decreased sample turnaround time for Class 1 residual solvents by 50%.
- DB-624 Column: The Agilent DB-624 column in the 0.45 mm id provides superior resolution, low bleed, and high capacity for the complex mixture and wide concentration range encountered for Class 1 and Class 2 solvents.

Discussion

Low-level residual solvents are typically determined by gas chromatography (GC) coupled with a flame ionization detector (FID) and a static headspace sampling device. Figure 1 shows a chromatogram of a standard solution of Class 1 and Class 2 residual solvents at the allowed limit concentrations as defined by the ICH (between 2 and 5,000 ppm). Pharmaceutical quality control laboratories currently face a number of instrument-related issues:

- The area precision in HS analysis can be compromised primarily due to atmospheric pressure variations influencing the amount of analytes injected from the loop in a gas sampling valve (GSV).
- The sensitivity is low for some low-concentration analytes (for example, benzene).
- Sample turnaround time/analysis time is excessive and caused by late-eluting impurities and high-boiling solvents/diluents (such as 1,3-dimethyl-2-imidazolidinone [DMI] with a boiling point of 225 °C).

New capillary flow technology and state-of-the-art pneumatic electronics implemented in the 7890A GC addresses these issues and significantly improves the analysis of residual solvents. Figure 2 shows a block diagram of the HS/VI/GC/FID system. The HS transfer line is interfaced to the GC by a volatiles interface (VI), which is operated at 2:1 split ratio for improved sensitivity. The sample pressure in the gas sampling valve loop of the HS sampler is controlled to within 0.001 psi by an electronic backpressure regulator (BPR) to significantly improve area precision. This function is part of the dual mode Programmable Control Module (PCM) on the 7890A GC. Sensitivity is also improved by pressurizing the sample in the loop of the GSV. Finally, implementation of a column backflush facilitated by a capillary-flow-technology splitter and aided by fast oven cool-down time decreases the sample turnaround time; this is shown in Figure 3. Figure 4 shows typical repeatability in peak area and retention time and the Method Detection Limit (MDL) for o-xylene as a representative example. [1]



1. Methanol
2. 1,1 Dichloroethylene
3. Acetonitrile
4. Methylene chloride
5. Trans 1,2 dichloroethene
6. Hexane
7. Cis 1,2 dichloroethene
8. Nitrobenzene (co-elute with 7)
9. Trichloromethane
10. Carbon tetrachloride
11. Cyclohexane (co-elute with 10 and 12)
12. 1,1,1 trichloroethane (co-elute with 10 and 11)
13. Benzene
14. 1,2 dimethoxyethane
15. 1,2 dichloroethane
16. Trichloroethylene
17. Methyl cyclohexane
18. 1,4 dioxane
19. Pyridine
20. Toluene
21. 2 hexanone
22. Chlorobenzene
23. Ethylbenzene
24. DMF
25. M-xylene
26. P-xylene
27. O-xylene
28. N,N dimethylacetamide
29. Tetralin

Figure 1. Class 1 and Class 2 residual solvents.

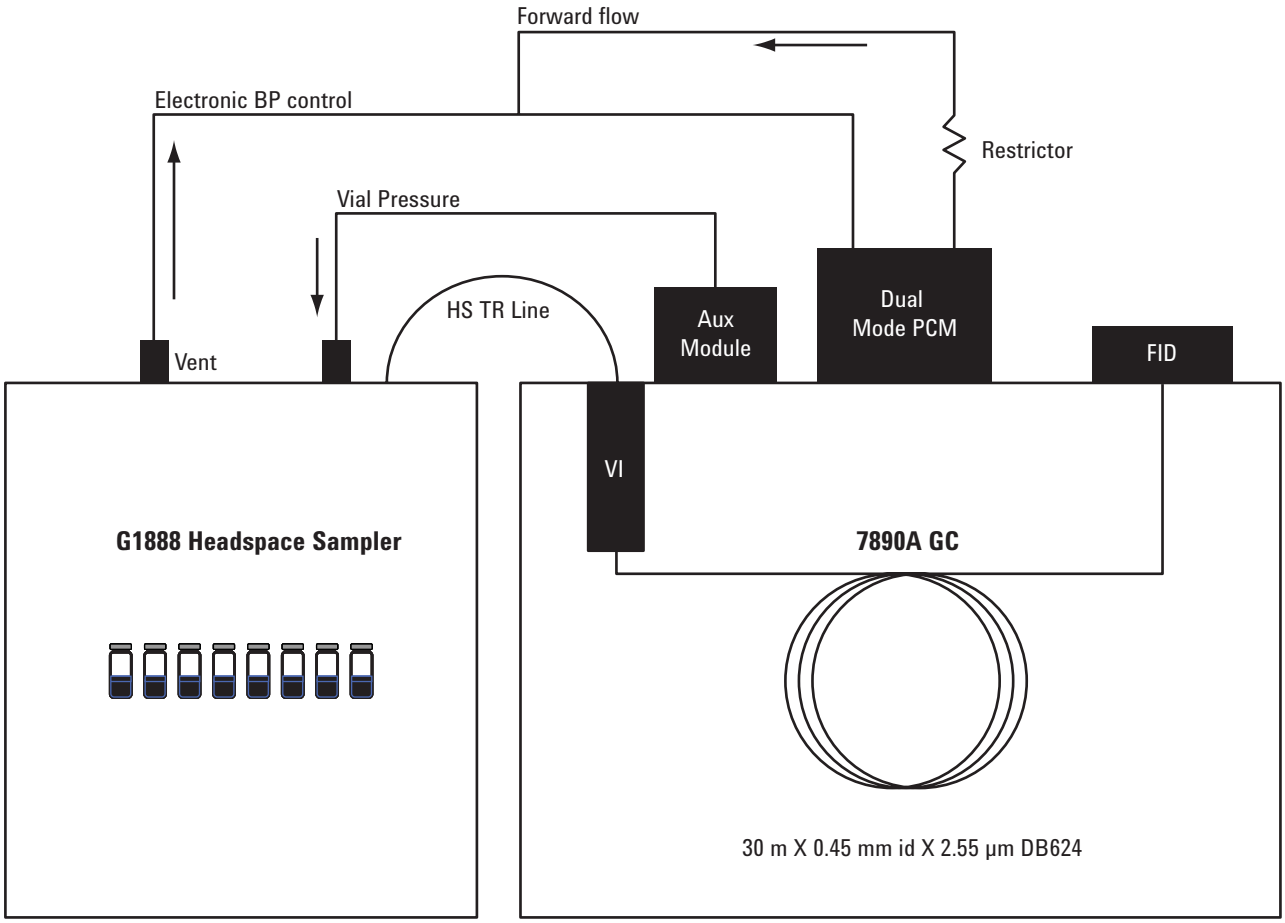


Figure 2. Block diagram of residual solvents configuration without backflush.

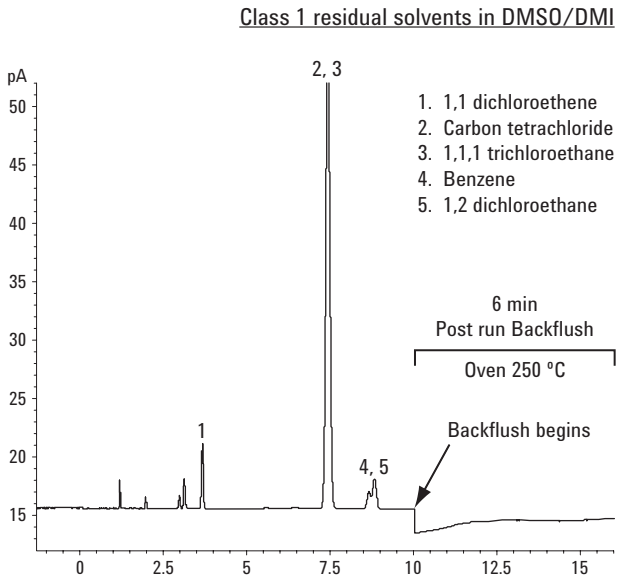


Figure 3. Backflush of Class 1 residual solvents in DMSO/DMI.

t_R = 23.251 +/- 0.001 min
@ 99 % Confidence level
RSD_{Area} = 2 %
Method detection limit = 9.8 ppm [1]

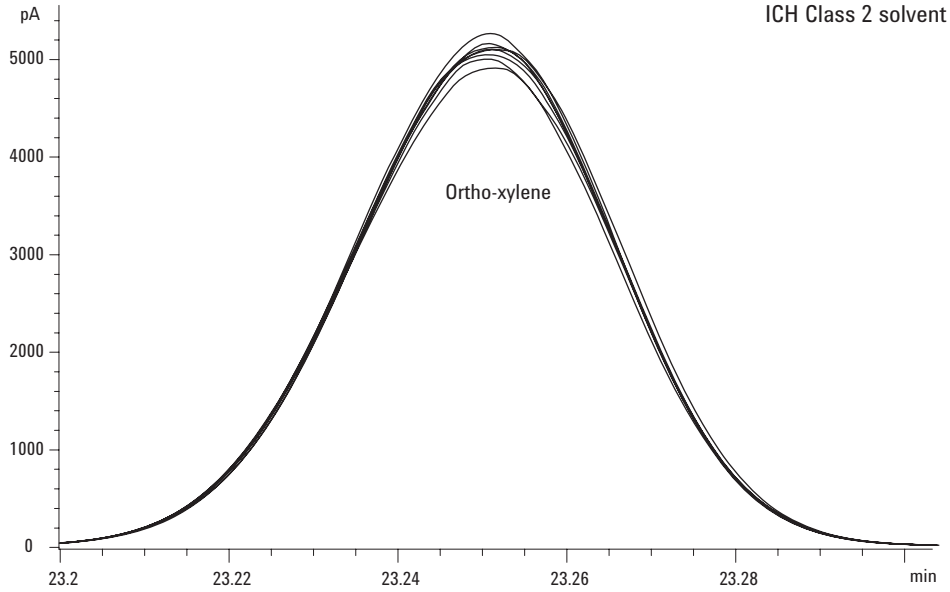


Figure 4. O-xylene (195 ppm), overlay N = 8 (BPR of HS loop @ 5 psi, HS vial pressurized to 20 psi).

References

1. Statistical MDL = s * t(n-1, 1-alpha = 99) = s * 3.143, where (n-1,1-alpha) = Student's t value for the 99% confidence level with n-1 degrees of freedom. N = number of trials, s = standard deviation of the 7 trials. US EPA Method 524.2, Revision 4, 1992.

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