AD-0018-GC

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GCMS

October 2006

Static headspace-GC analysis of ten residual solvents in water by using Shimadzu GC-2010 combined with Teledyne Tekmar HT3 static/dynamic headspace auto-sampler. Part 1. Precision of Analysis.

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Introduction

Residual solvents present in bulk or finished pharmaceuticals are commonly analyzed according to the procedures specified in an international standard, such as the United States Pharmacopeia (USP). The USP 29 Chapter <467> describes the analysis method by using static headspace-gas chromatography with flame ionization detector. Although the chapter also describes other analytical procedures that may be used where specified in the individual monographs, the headspace operating parameters described in the main procedures indicate the use of automatic headspace sampler with a sample transfer line.

Shimadzu GC-2010 gas chromatograph can be combined with the Teledyne Tekmar HT3 Static/Dynamic Headspace Sampler, which is an automated headspace sampler that uses a transfer line for transferring the headspace to the gas chromatograph. We used the static option of the headspace auto-sampler in the present work.

Precision of the response (i.e. peak area) is one of the main parameters used in validating a system or in any quantitative routine work. We analyzed ten organic solvents at two concentration ranges to demonstrate the precision of the above system, namely of 2 to 5 µg/mL and 100 to 300 µg/mL. From the experiments that we have carried out both in our Singapore and India laboratories, we found that the %RSD values are within the USP specification of no more than 15%.

Experimental

Table 1. Instrument Parameters

HT3 Parameters		GC-2010 Parameters	
Constant Heat Time	On	**Injection Port [SPL]**	
GC Cycle Time	45.00 min	Injection Mode	Split
Valve Oven Temp.	85 °C	Injection Temp.	140 °C
Transfer Line Temp.	85 °C	Carrier Gas	Helium (99.999%)
Standby Flow Rate	50 mL/min (Helium 99.999%)	Flow Control Mode	Velocity
Platen/Sample Temp.	80 °C	Pressure	25.0 kPa
Platen Temp Equil. Time	1.00 min	Column Flow	4.86 mL/min
Sample Equil. Time	60.00 min	Linear Velocity	35.0 cm/sec
Mixer	Off	Purge Flow	3.0 mL/min
Mixing Time	5.00 min	Split Ratio	5.0
Mixing Level	Level 5	Column	Rtx-1301, 30 m length, 0.53 mm ID, 3.00 µm thickness [Restek Corp.]
Mixer Stabilize Time	0.50 min	Column Oven Temp. Program	40 °C (20 min) - 20 °C/min - 240 °C
Pressurize	9 PSIG	**Detector [FID]**	
Pressurize Time	1.50 min	Temperature	250 °C
Pressurize Equil. Time	0.20 min	Sampling Rate	40 msec
Loop Fill Pressure	3 PSIG	Make-up Gas	Nitrogen
Loop Fill Time	2.00 min	Make-up Flow	30 mL/min
Inject Time	1.00 min	Hydrogen Flow	40 mL/min
		Air Flow	400 mL/min

Sample Preparation Procedure

Standard stock solution A - Weigh 97 mg of acetone, 98 mg of isopropanol, 94 mg of acetonitrile, 41 mg of dichloromethane, 37 mg of n-hexane, 69 mg of chloroform, 38 mg of benzene, 50 mg of trichloroethylene, 106 mg of n-butanol, and 39 mg of toluene, and dilute to 20 mL of total volume using dimethylformamide.

Test solutions A (2 to 5 µg/mL) - Dilute stock solution A 1:1000 in water. That is, for a 50 mL test solution, dilute 50 µL of stock solution into 50 mL using organic-free water. [Tip: to dispense 50 µL of the stock solution more accurately, use a 100 µL gas-tight microsyringe, withdraw 70 µL of stock solution, and dispense up to 20µL mark.] Then pipet 5.0 mL aliquots of the test solution into individual 22 mL headspace vials. Seal the vials immediately by using septa and crimp caps [Note: vials, septa and caps were obtained from Teledyne Tekmar]. Verify the goodness of seal of each vial manually by twisting the cap by hand; the cap must not be able to turn when twisted.

Standard stock solution B - Weigh 1,019 mg of acetone, 1,040 mg of isopropanol, 1,000 mg of acetonitrile, 532 mg of dichloromethane, 506 mg of n-hexane, 532 mg of chloroform, 517 mg of benzene, 522 mg of trichloroethylene, 1,522 mg of n-butanol, and 503 mg of toluene, and dilute to 50 mL of total volume using dimethylformamide.

Test solutions B (100 to 300 µg/mL) - Dilute stock solution B 1:100 in water. That is, for a 50 mL test solution, dilute 0.5 mL of stock solution into 50 mL using organic-free water. [Tip: use a 1 mL or 2 mL gas-tight microsyringe]. Then pipet 5.0 mL aliquots of the test solution into individual 22 mL headspace vials. Seal the vials immediately by using septa and crimp caps [Note: vials, septa and caps were obtained from Teledyne Tekmar]. Verify the goodness of seal of each vial as described above.

Gas chromatography

As in any static headspace analysis, the repeatability of the data is checked by analyzing between three to six test samples, each contained in a sealed gas tight vial, each having equal volume of sample and each having the same concentrations of analytes. Each of the batches of test samples that we reported here consists of 5 test samples (i.e., n = 5), which were analyzed sequentially.

Table 2. Analytes investigated and the batch to batch reproducibility. Concentrations are rounded to 1 significant figure. ACT = acetone (5.0 µg/mL), IPA = isopropanol (5.0 µg/mL), ACN = acetonitrile (5.0 µg/mL), DCM = dichloromethane (2.0 µg/mL), HXN = n-hexane (2.0 µg/mL), CFM = chloroform (3.0 µg/mL), BZN = benzene (2.0 µg/mL), TCE = trichloroethylene (3.0 µg/mL), BuOH = n-butanol (5.0 µg/mL), TOL = toluene (2.0 µg/mL).

	%RSD									
Batch	ACT	IPA	ACN	DCM	HXN	CFM	BZN	TCE	BuOH	TOL
1 (n=5)	2.3	3.4	3.1	1.0	0.5	0.9	0.7	0.6	2.8	0.7
2 (n=5)	1.6	2.1	1.5	1.1	1.1	0.8	0.8	0.7	1.6	0.8
3 (n=5)	1.3	2.8	1.8	2.0	3.7	2.0	2.0	2.2	2.5	2.1
4 (n=5)	1.3	2.8	1.9	1.2	1.7	1.1	1.2	1.4	3.4	1.3
5 (n=5)	1.0	2.5	1.9	1.0	1.3	0.9	0.9	1.0	1.7	0.9
6 (n=5)	2.5	1.9	2.0	2.0	4.0	2.2	2.1	2.0	2.7	2.4
7 (n=5)	1.6	3.0	2.2	1.0	0.6	0.9	0.8	0.7	3.8	0.8
8 (n=5)	3.3	3.6	2.8	1.6	0.7	1.3	1.2	0.9	4.4	1.1
9 (n=5)	1.1	1.9	1.3	0.9	1.3	1.0	0.9	1.0	1.8	0.9
10 (n=5)	1.9	2.4	1.8	1.7	2.2	1.7	1.8	2.0	3.5	1.7

Table 3. Analytes investigated and the batch to batch reproducibility. Concentrations are rounded to 1 significant figure. ACT = acetone (200 µg/mL), IPA = isopropanol (200 µg/mL), ACN = acetonitrile (200 µg/mL), DCM = dichloromethane (100 µg/mL), HXN = n-hexane (100 µg/mL), CFM = chloroform (100 µg/mL), BZN = benzene (100 µg/mL), TCE = trichloroethylene (100 µg/mL), BuOH = n-butanol (300 µg/mL), TOL = toluene (100 µg/mL).

	%RSD									
Batch	ACT	IPA	ACN	DCM	HXN	CFM	BZN	TCE	BuOH	TOL
1 (n=5)	2.6	2.3	2.8	1.6	7.5	1.9	2.1	2.5	2.3	2.2
2 (n=5)	1.4	1.6	1.1	1.0	3.7	1.2	1.3	1.6	1.6	1.3
3 (n=5)	2.6	4.3	3.4	2.6	6.5	3.0	3.3	3.9	4.3	3.3
4 (n=5)	1.5	3.0	2.6	1.8	5.4	2.1	2.5	2.8	2.9	2.1
5 (n=5)	1.2	1.5	1.6	2.0	5.0	2.3	2.6	2.9	1.6	2.5
6 (n=5)	4.0	3.9	2.9	1.9	3.6	1.8	1.8	1.7	3.7	1.4
7 (n=5)	1.1	1.2	1.2	1.1	3.0	1.3	1.3	1.4	1.3	1.2

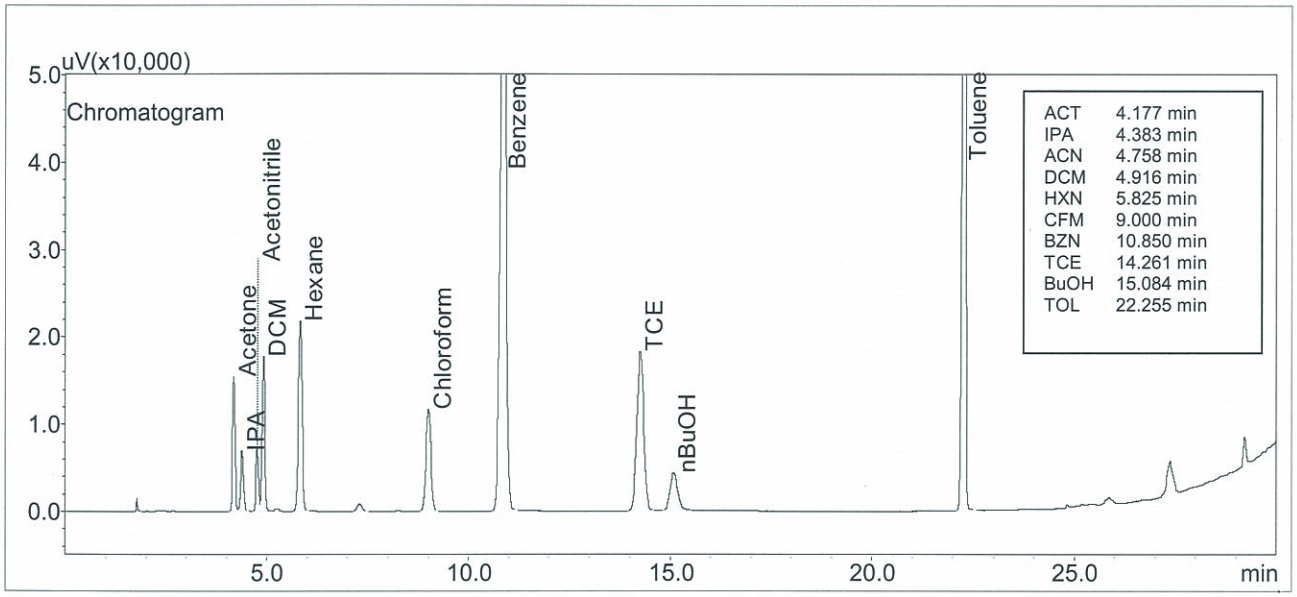

Figure 1. A representative chromatogram of the test sample analyzed (analyte conc. level between 2 to 5 µg/mL in solution).

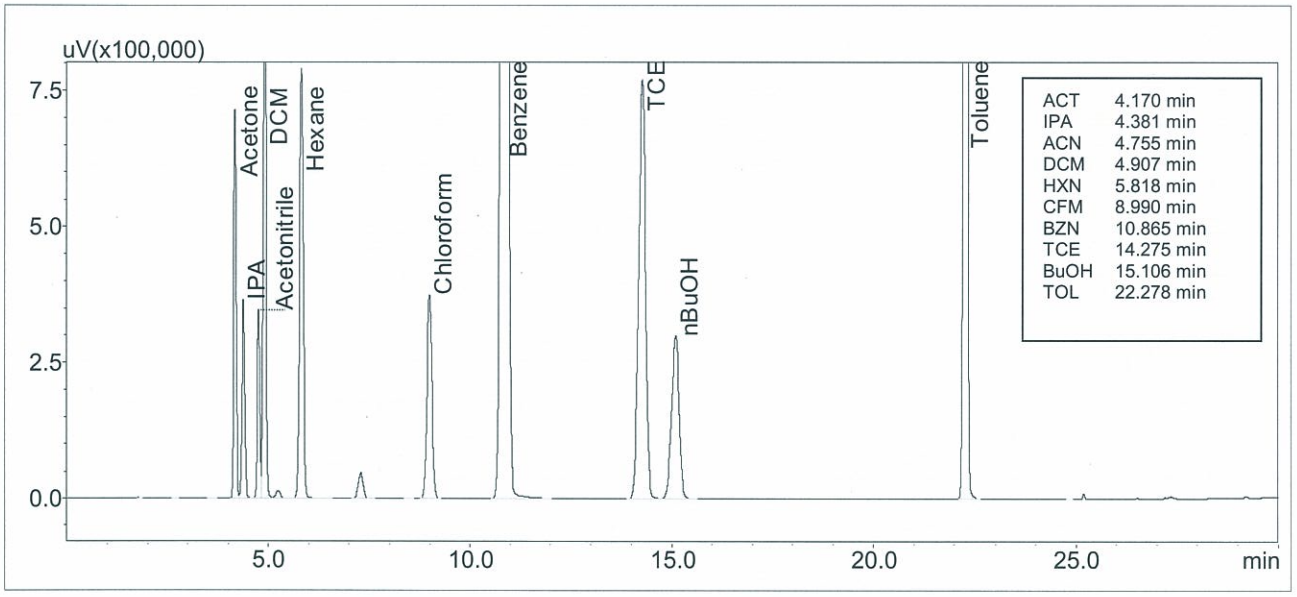

Figure 2. A representative chromatogram of the test sample analyzed (analyte conc. level between 2 to 5 µg/mL in solution).

Conclusion

The precision of headspace analysis by using Shimadzu GC-2010 gas chromatograph and Tekmar HT3 Headspace Autosampler was found to be satisfactory for the ten organic solvents investigated. %RSD values below the 15% limit specified by USP could be obtained reproducibly.

The Leak Check feature of the HT3 system, and the System History, which records the key pressures involved in the analysis, are particularly valuable in judging the condition of the whole system before and during the analysis, considering that the gas-tightness of the system, including the sealing of the headspace vials, is a very important factor in obtaining good repeatability and reproducibility in headspace analysis.

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[IPDL] Printed in Singapore.