SHIMADZU APPLICATION NEWS

LAAN-A-G-E003

● GAS CHROMATOGRAPHY

No.G223

Analysis of Residual Solvents in Pharmaceutical Products (Part 6)

Comparison of Headspace GC Sensitivity depending on Dilution Solvents (Class 3 Solvents)

■ Headspace Gas Chromatography for Class 3 Solvents

There are two methods of analyzing residual solvents in pharmaceuticals: a method where the pharmaceutical is dissolved in a solvent and the solution is directly injected to GC, and a method where the solution is enclosed and heated in a vial and the evaporated gas phase is analyzed by GC. The latter method is called the headspace GC.

In headspace GC, the sensitivity to the target solvent components largely depends upon the degree to which they evaporate into the gas phase by being heated in the vial.

The amount of components evaporating into the gas phase differ depending on the type of solvent used to dissolve the pharmaceutical (dilution solvent in the case of standard solution), due to the difference in solubility of the target components in the solvent.

Application News G209 introduced an example of analyzing Class 1 and 2 solvents to investigate the differences in sensitivity depending on the dilution solvent used for analysis. This Application News introduces analysis of some Class 3 solvents.

The dilution solvents examined were water (stipulated in the USP and EP), DMSO (stipulated in the USP), and DMF (stipulated in the EP). These solvents were also used in Application News G209.

For each component, a standard solution of 100ppm concentration was enclosed and heated in a vial. The heating conditions were: 80˚C and 60minutes for water and DMSO (specified in the USP, specified in the EP for water), and 105˚C and 45minutes for DMF (specified in the EP).

Table 1 shows the relative sensitivity, with the peak area for each component taken to be 1 when water is used as the dilution solvent. ([>1] indicates greater sensitivity than water, and [1/100>] indicates sensitivity below 1/100th that of water.)

The analytical conditions are shown in Table 2. (The same conditions as Shimadzu Application News G209.)

Table. 1 Relative Sensitivity when Using DMF or DMSO (Compared to Water)

	DMSO				DMF			
Class 3	>1	>1/10	>1/100	1/100>	>1	>1/10	>1/100	1/100
Pentane(C5)		○				○		
Ethanol(EtOH)								
Ethyl ether(DEE)		○				○		
Acetone(Actn)		○				○		
2-Propanol(IPA)		○				○		
Methyl Acetate (MeAc)		○				○		
tert-Butylmethyl ether(MTBE)		○				○		
1-Propanol(nPrOH)			○			○		
Methylethylketone(MEK)		○				○		
Ethyl acetate(EtAc)			○			○		
2-Methyl-1-propanol(isoBuOH)			○			○		
Isopropyl acetate(isoPrAc)			○				○	
Heptane(C7)			○				○	
1-Butanol(nBuOH)			○			○		
Propyl acetate(nPrAc)			○				○	
Methylisobutylketone(MiBK)			○				○	
3-Methyl-1-butanol(isoAmOH)				○			○	
Isobutyl acetate(isoBuAc)			○				○	
1-Pentanol(nAmOH)				○		○		
Butyl acetate(nBuAc)			○		○		○	

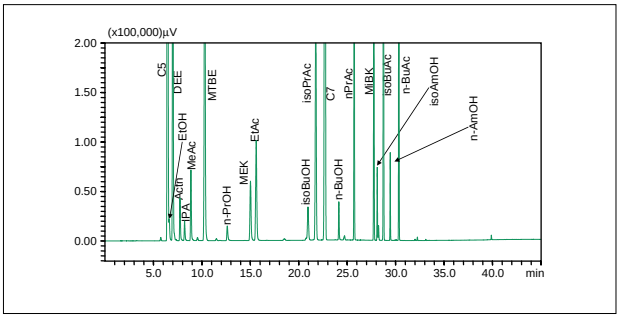
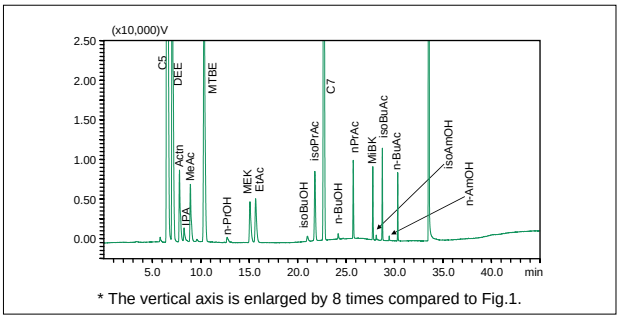
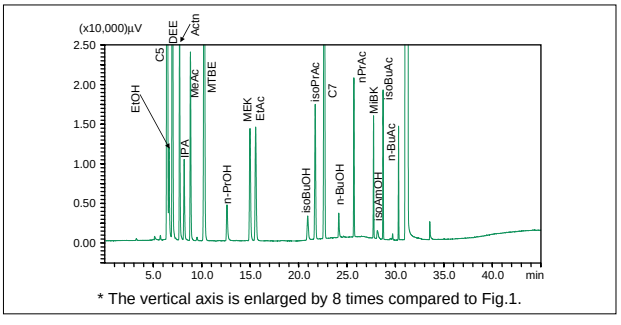


Fig. 1 HS Gas Chromatogram of Class 3 Solvents in Water



* The vertical axis is enlarged by 8 times compared to Fig.1.

Fig. 2 HS Gas Chromatogram of Class 3 Solvents in DMSO



* The vertical axis is enlarged by 8 times compared to Fig.1.

Fig. 3 HS Gas Chromatogram of Class 3 Solvents in DMF

■ Headspace Gas Chromatograms of DMF and DMAc in Water and DMI

The European Pharmacopoeia (EP) section 2.4.24 “Identification and Control of Residual Solvents” specifies the following three dilution solvents.

- Sample preparation 1 (Pharmaceuticals soluble in water)
  Dilution solvent : Water; heat at 80˚C for 60minutes
- Sample preparation 2 (Pharmaceuticals insoluble in water)
  Dilution solvent : DMF; heat at 105˚C for 45minutes
- Sample preparation 3 (solvent component to be analyzed is DMF or DMAc)
  Dilution solvent : 1,3-dimethyl-2-imidazolidinone (DMI); heat at 80˚C for 45minutes

DMF and DMAc (100ppm each) were analyzed in water and DMI solvents. The water solution was heated at 80˚C for 60minutes, and DMI solution 80˚C for 45minutes, and the headspace was analyzed. Fig.4 shows the obtained chromatograms. DMF and DMAc were not detected in the water solution, while they were detected in the DMI solution.

The column used in this analysis was a DB-WAXETR (50m × 0.32mm I.D., film thickness 1.0µm). The other analytical conditions were in accordance with Table 2.

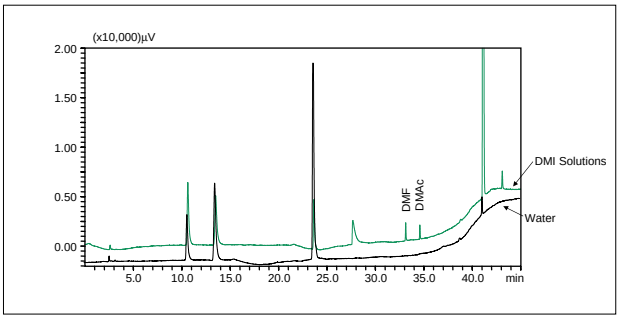


Fig.4 Chromatograms of DMF and DMAc in Water and DMI Solutions

■ Headspace Gas Chromatograms of Solvents in DMI Solution

The Class 1 and 2 solvents introduced in Application News G209, and the Class 3 solvents analyzed above were analyzed by headspace GC using DMI as the dilution solvent. The obtained chromatograms are shown below. The analytical conditions are shown in Table 2 (the same as G209).

Apart from DMF and DMAc, which were already analyzed above, there were no components that could achieve a particularly good sensitivity when using DMI, compared to when using other dilution solvents. (Tetrachloromethane (CCl4) was virtually undetected with DMI.)

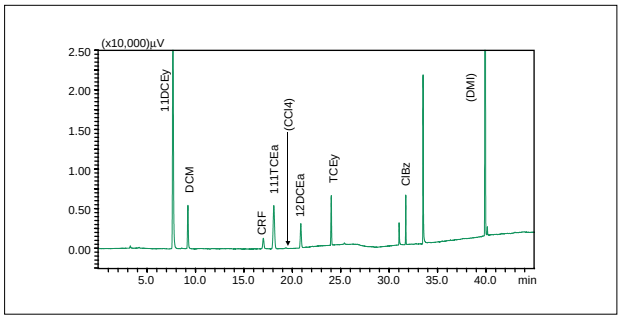


Fig.5 Chromatogram of Class1 and Class2 Chlorinated Solvents in DMI

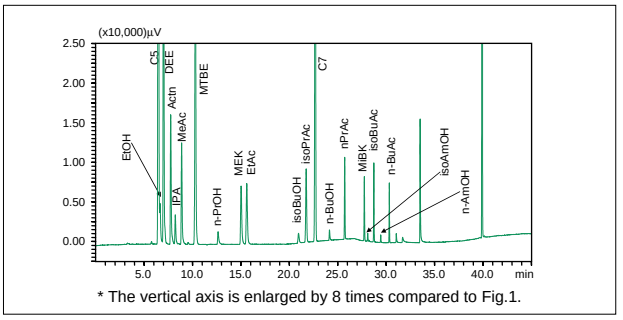


Fig.7 Chromatogram of Class3 Solvents in DMI

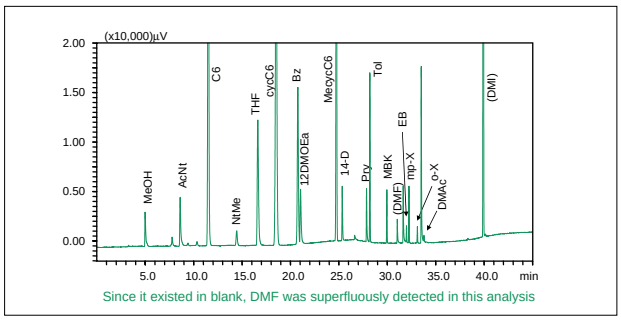


Fig.6 Chromatogram of Class1 and Class2 Non-Chlorinated Solvents in DMI

Table 2 Analytical Conditions

Model	: TurboMatrix HS-40 + GC-2010
Column	: DB-624 60m × 0.32mmI.D. df: 1.8µm
	(Fig.4 only)DB-WAXETR 50m × 0.32mmI.D. df: 1.0µm
Column Temp	: 40˚C(20min)-10˚C/min-240˚C
Inj.Temp.	: 140˚C, Det Temp. : 260˚C
Carrier Gas	: He, 35cm/sec, Split Ratio : 1:5
Sample	: 80˚C 60min (in Water, in DMSO)
Thermostatting	: 110˚C 45min (in DMF)
	80˚C 45min (in DMI)
Headspace	: 1mL
Injection Volume	

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