SHIMADZU APPLICATION NEWS

LAAN-A-G-E006

● GAS CHROMATOGRAPHY

No.G228

Residual Solvents Analysis in Pharmaceutical Products (Part 7)
Thermostatting Dependencies of Aqueous Solution / Water Dilution Effect on DMSO Solution

In Shimadzu Application News No. G209 and G223, comparison was made for GC sensitivity depending on dilution solvent.
Since many of the residual solvents in pharmaceutical products do not easily dissolve in water, these solvents in aqueous solutions can be analyzed with relatively good sensitivity using headspace GC. Introduced here is the change in detection sensitivity due to changing of the thermostatted temperature of an aqueous solution. Also introduced here is an investigation of how detection sensitivity changes by the dilution of a DMSO solution using water.

■ Dependence of Sensitivities of Components in Solution on Thermostatting Temperature

Generally, in headspace GC, when the thermostatted temperature is increased, the detection sensitivity of volatile components increases.
However, the thermostatted temperature dependence varies according to the components, such that an increase in thermostatted temperature causes a sudden increase in sensitivity in some components, and merely a slight increase in other components.
Here, there is a comparison of the level of thermostatted dependence with respect to 20 typical organic solvents.
For the test samples, aqueous solutions were prepared containing 100ppm of the following typical organic solvents, respectively. 5mL of each of these solutions was enclosed into a vial, and after maintaining at temperatures of 80˚C, 95˚C and 120˚C for 60minutes each, they were analyzed by headspace GC.
- Organic Solvents Investigated-
methanol (MeOH), ethanol (EtOH), isopropanol (IPA), n-propanol (nPrOH), n-butanol (nBuOH), acetone (Actn), acetonitrile (AcNt), ethyl acetate (EtAc), n-propyl acetate (nPrAc), isopropyl acetate (isoPrAc), butyl acetate (nBuAc), isobutyl acetate (isoBuAc), chloroform (CRF), dichloromethane (DCM), DMF, DMSO, toluene (Tol), hexane (C6), 2-methoxyethanol (Mecel), 2-ethoxyethanol (Etcel)
Fig.1 shows the peak area for each of the components, where peak area ratios for 95˚C and 120˚C are graphed with the peak areas at 80˚C taken as 100.
All of the components show an increase in detection sensitivity with increases in thermostatted temperature, however, the ratios are different. With substances having comparatively high solubility in water, such as the glycol ethers and alcohols, it is possible to look for a tendency of high thermostatted temperature dependence.
Fig.2 and Fig.3 show the chromatograms at thermostatted temperatures of 80˚C and 120˚C, respectively. Table 1 shows the analytical conditions.

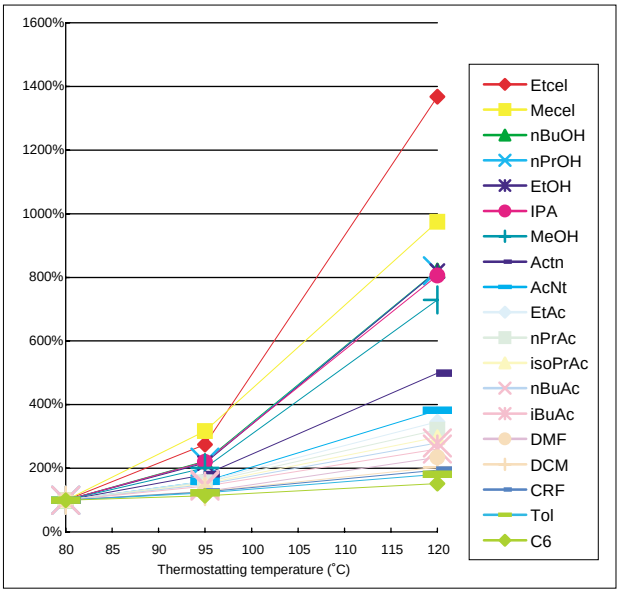

Fig. 1 Dependence on Thermostatting Temperature of Components in Aqueous Solution

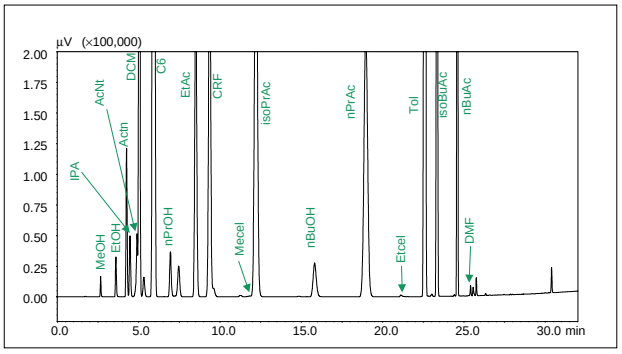

Fig. 2 Headspace Gas Chromatogram of Aqueous Solution Kept at 80˚C for 60Minutes

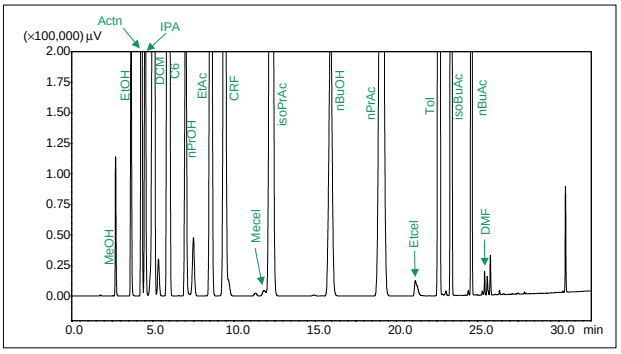

Fig. 3 Headspace Gas Chromatogram of Aqueous Solution Kept at 120˚C for 60Minutes

Table 1 Analytical Conditions

Model	: TurboMatrix HS-40 + GC-2010	Carrier Gas	: He, 35cm/sec
Column	: Rtx-624 30m × 0.53mm I.D. film: 1.8µm	Sample Thermostatting	: 80, 95, 120˚C, 60min (Fig.1~3)
Column Temp	: 40˚C(20min)-20˚C/min-240˚C		80˚C 60min (Fig.5~7)
Inj.Temp.	: 170˚C, Det Temp. : 250˚C		

■ Dependence of the Sensitivities of Components in DMSO Solution on Dilution with Water

As introduced in Shimadzu Application News No. G209 and G223, many of the residual solvents in pharmaceutical products can be analyzed with relatively good sensitivity using headspace GC when they are placed in aqueous solution. This is because these solvents have lower solubility in water than in DMSO, DMF and DMI, making it easier for them to enter the gas phase.

Therefore, if the pharmaceutical product to be analyzed can be dissolved in water, it could be said that placing it in aqueous solution for analysis would be ideal. However, for samples that are not soluble in water, this is not the case.

At this point, it is logical to investigate the effect of first dissolving a water-insoluble pharmaceutical product in an appropriate solvent, and then diluting that solution with water.

Assuming a pharmaceutical product that is "water insoluble, DMSO soluble", we first prepared the DMSO solution, and after diluting it with water, we investigated the change in detection sensitivity of residual solvents.

As shown in Fig.4, a 100ppm DMSO solution of organic solvent (ratio of water: 0%) was stepwise diluted with water (water ratios: 20%, 50%, 80%), and 5mL of each of these was enclosed in a vial. They were kept at same temperature then analyzed in the same way by headspace GC.

Fig.5 is a graph showing the peak area as 100 for each component at a water ratio of 0%, and the respective peak area ratios at water ratios of 20%, 50% and 80%, respectively.

If there were an organic solvent that were similarly volatile in either aqueous solution or DMSO solution, the concentration in the solution would decrease as the DMSO solution is diluted, so the peak area values should decrease proportionally. (For example, MeOH shows behavior that approaches this.)

However, with most organic solvents, in the case of a 50% water ratio solution, regardless of the fact that the concentration of each component in solution is 50ppm, they are detected as larger peaks than when the water ratio is 0% (the concentration is 100ppm).

In particular, in the case of compounds like chloroform (CRF), in which the solubility in water and in DMSO differs greatly, an increase of more than 10 times the sensitivity is acknowledged.

Fig.6 and Fig.7 show the headspace gas chromatograms using water ratios of 0% and 50%, respectively. The analytical conditions are shown in Table 1.

These results suggest that it may be worthwhile considering "dilution with water of a solution containing a dissolved solvent" as a means of increasing sensitivity in HS-GC.

Caution) Since adding water to DMSO solution generates heat, to prevent the organic solvent from volatilizing, it is necessary to be careful during vial enclosure.

In addition, this experiment was conducted using a standard solution for dissolving each component in the DMSO solution. When actually dissolving a pharmaceutical product in DMSO solution, addition of water may cause precipitation of another component or other such problems.

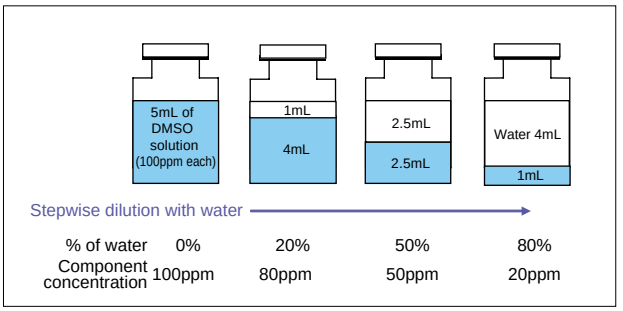

Fig. 4 Stepwise Dilution of DMSO Solution with Water

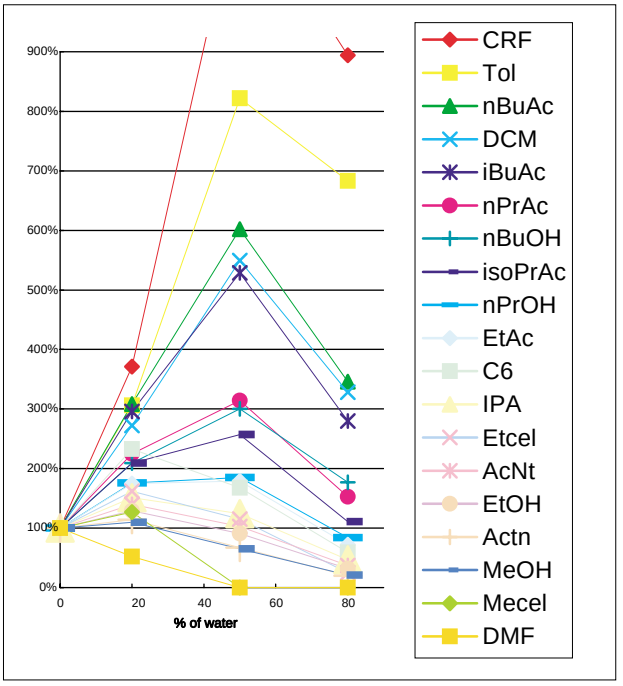

Fig. 5 Sensitivity Changes when DMSO Solution was Diluted with Water

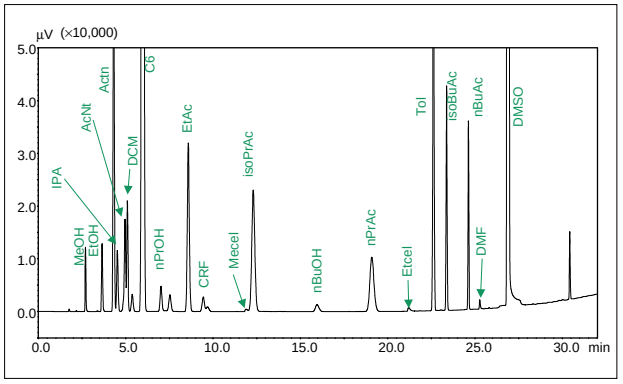

Fig. 6 Headspace Gas Chromatogram when Water% is 0

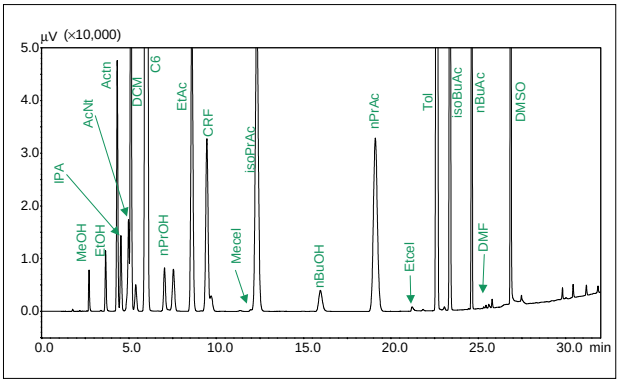

Fig. 7 Headspace Gas Chromatogram when Water% is 50

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