USP <467> residual solvent analysis

Application Notes #283029

The Analysis of Residual Solvents By Headspace Sampling and GC According to USP <467>

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are consumed or produced in the manufacture of drug products.

Appropriate selection of the solvent for the synthesis of a drug substance may enhance the yield, or determine characteristics such as crystal form, purity and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. Residual solvents are not completely removed by practical manufacturing techniques. The United States Pharmacopeia (USP) <467> specifies the gas chromatographic conditions[1] for the analysis of these organic volatile impurities (OVI).

This application note describes the gas chromatographic analysis of these residual solvents combined with the headspace sampling and injection technique.

Instrumentation

456-GC Gas Chromatograph

- Injector: Split/Splitless, 1177 S/SL, full EFC control
- Detector: FID, full EFC control

Headspace Sampler

- SHS-40 Headspace Analyzer

GC control and data handling

- compassCDS software

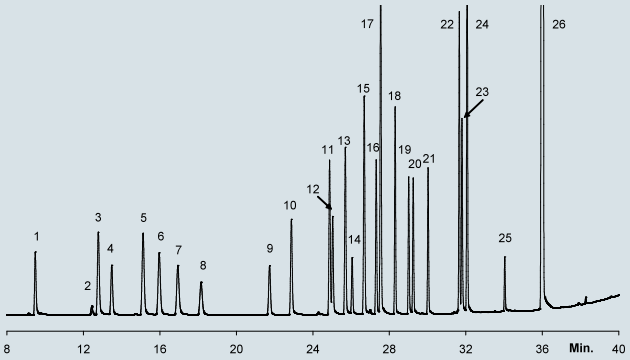
Sample Preparation

Solvents ranging in concentration from 100 to 500 ppm (v/v) from a stock solution were added to de-ionized water and serial dilutions prepared from the resulting mixture were used to calibrate the system.

Table 1. Peak Identification.

#	Component	#	Component
1	Methanol	14	Trichloromethane
2	Pentane	15	Cyclohexane
3	Ethanol	16	Benzene
4	Diethylether	17	2-Methylpropanol
5	Acetone	18	Heptane
6	2-Propanol	19	Trichloroethylene
7	Acetonitrile	20	1-Butanol
8	Dichloromethane	21	1,4-Dioxane
9	Hexane	22	Methylisobutylketone (MIBK)
10	1-Propanol	23	Pyridine
11	Methylethylketone (MEK)	24	Toluene
12	Ethylacetate	25	N,N-Dimethylformamide
13	Tetrahydrofuran (THF)	26	Dimethylsulfoxide (DMSO)

Figure 1. Chromatogram of a water sample spiked with "residual solvents".



Instrument Operational Conditions

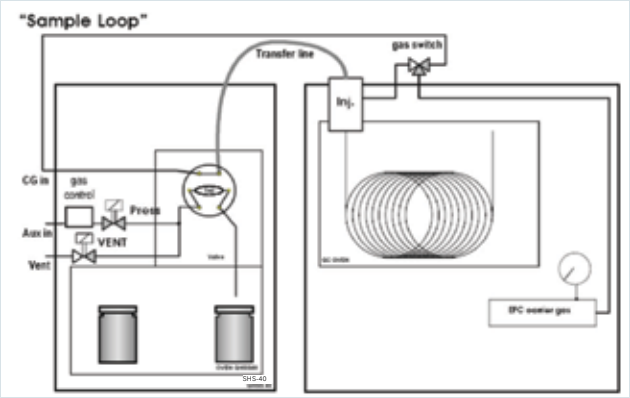
SHS-40 Automated Headspace Sampler

Type:	Sample loop
Oven:	80°C
Valve:	180°C
Tube:	180°C
Precond. time:	60 min. shaking
Run time:	45 min.

450-GC Gas Chromatograph

Column:	GC Care Column: BR-624ms fs, 60m x 0.32mm, df= 1.80 µm PN: BR86128
Injector:	200°C, Split ratio 1:10
Detector:	FID, 270°C
Carrier Gas:	He, 1mL/min. constant flow
Oven:	40°C, 20 min. isothermal @ 10°C/min. to 250°C

Figure 2. Connection scheme of the SHS-40 and the 450-GC.



Results and Discussion

The system is validated using five independently spiked water samples at different concentrations using the 26 component standard/stock solution used to prepare the calibration standard. A typical chromatogram of the 26 components is shown in Figure 1. The hardware configuration is shown schematically in Figure 2.

Concentrations range between 100 and 500 ppm per component. Calibration curves were then generated for each individual component. Figures 3 – 6 below show several selected solvents with different polarity that represent examples of the different safety classes stated in the method.

Figure 3. Calibration curve of Pentane.

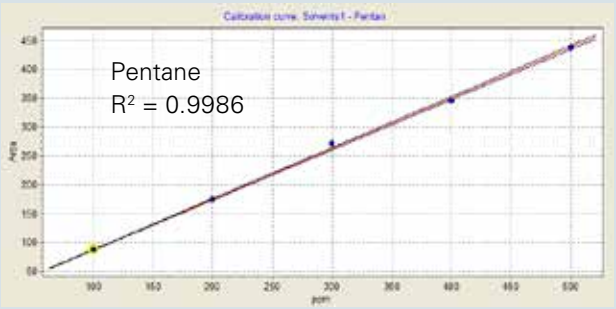


Figure 4. Calibration curve of Benzene.

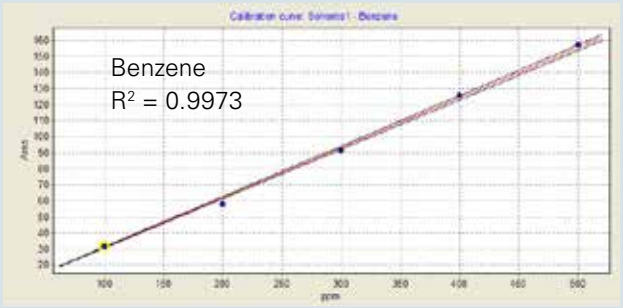


Figure 5. Calibration curve of Dichloromethane.

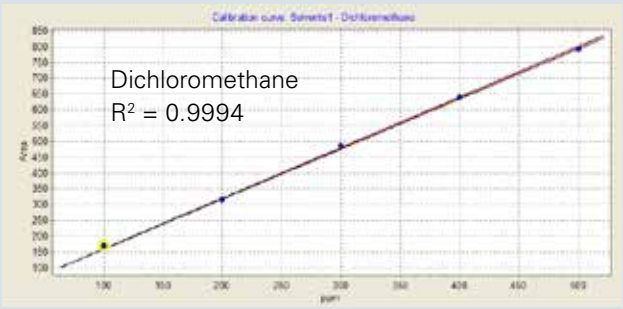
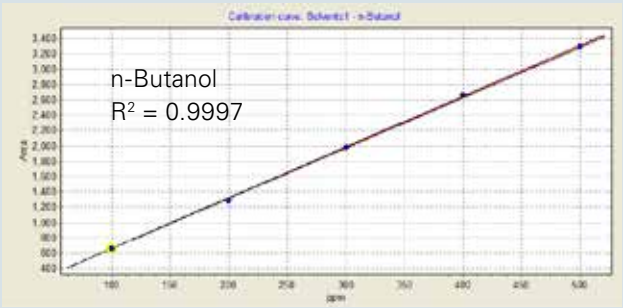


Figure 6. Calibration curve of n-Butanol.



The calibration curves shown above clearly indicate that the system is well suited for the analysis of the different solvent types.

Table 2. Correlation Coefficient per compound.

Safety Class 1

Compound	Correlation coefficient
Benzene	0.9973

Safety Class 2

Compound	Correlation coefficient
1,4-Dioxane	0.9903
Acetonitrile	0.9887
Cyclohexane	0.9996
Dichloromethane	0.9994
Methanol	0.9979
n-Hexane	0.9982
Pyridine	0.9954
Toluene	0.9997
Trichloroethylene	0.9957
Trichloromethane	0.9996

Safety Class 3

Compound	Correlation coefficient
1-Propanol	0.9905
2-Methylpropanol	0.9997
2-Propanol	0.9867
Acetone	0.9870
Diethylether	0.9995
Ethanol	0.9916
Ethylacetate	0.9970
Methylethylketone (MEK)	0.9989
Methylisobutylketone (MIBK)	0.9992
n-Butanol	0.9997
n-Heptane	0.9996
Pentane	0.9986
Tetrahydrofuran (THF)	0.9766

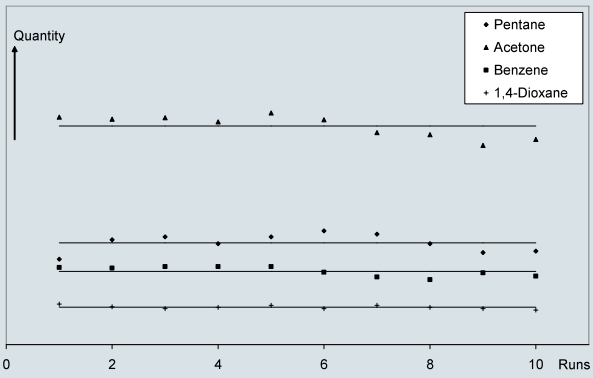
Correlation coefficients are close to 1.0 indicating a linear relationship between component concentration in the sample and detector signal. This indicates that the full system including headspace sampling, injection, separation and detection worked correctly.

Excellent correlation coefficients were achieved over a wide range of polarity including a-polar solvents like pentane, polar solvents like n-butanol, chlorinated solvents like dichloromethane and aromatic solvents like toluene.

However, further analysis improvements can be achieved if a salt like sodium sulfate is added to the samples. This ensures super saturation and forces the maximum amount of analyte into the headspace.

To further validate the system analysis to analysis, repeatability was tested. Some of the data is summarized in Chart 1. As before, the selected components are indicative of the different chemical classes and safety classes outlined in the method. The repeatability data shown in Chart 1 is excellent. Relative standard deviation is typically <5% for all components.

Chart 1. Repeatability data for selected components at 100 ppm level.



Conclusion

The combination of the Scion 456-GC Gas Chromatograph and Scion SHS-40 headspace sampler is well suited for the determination of residual solvents according to the United States Pharmacopeia (USP) <467>.

All components listed in the method show linear response in the analysis range and excellent system repeatability.

References

1. Organic Volatile Impurities / Residual Solvents <467>, United States Pharmacopeia USP 32-NF 18.

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