「Application Note」

# Analysis of Residual Solvents by ChroZen GC with Headspace According to USP 467

- GC Application


## Abstract

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Because residual solvents have no therapeutic benefits but harmful effects to human body if they remain in the final products, it is required to regulate these compounds not to exceed the specific limits defined in certain regulations.

United Stated Pharmacopeia (USP) classifies the residual solvents as following classification* depending on their risk to human health and defines Class 1 and Class 2 residual solvents as strongly restricted solvents.

In this study, the determination of residual solvents (Class 1 & 2) in pharmaceutical products by ChroZen GC/FID with Headspace was conducted according to the method (Procedure A) specified in USP 467.

*Class Ⅰ : Solvents to be avoided (Known as human carcinogens or strongly suspected human carcinogens and Environmental hazards)

Class Ⅱ : Solvents to be limited (Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.)

## Instruments and Software

| item | Description | Part No. |
|---|---|---|
| Oven | ChroZen GC Mainframe Assembly with UPC Detector Board Unit | 6701012502 |
| Inlet | Capillary Inlet Assembly for ChroZen GC | 6701012550 |
| Detector | FID Assembly for ChroZen GC | 6701012590 |
| ChroZen PAL RSI (Static Headspace) | ChroZen PAL RSI 850 Autosampler with headspace option | 6501011600 |
| | Mounting Kit for ChroZen GC | PAL3-Kit-YL6700 |
| CDS | YL-Clarity software for single instrument of YL GC | 5301011020 |
| | Autosampler control of YL-Clarity | 5301011040 |
| Column | Rxi-624Sil MS | 13870 |
| Install. Option | Start-up kit | 1601011110 |
| Acc | ChroZen PAL System Vial 20CV, 20mL Clear Glass Pk of 100 Pcs | Vial-20-ND18-CG-100 |
| | ChroZen PAL System Screw Cap 10CV and 20CV, Pk of 100 pcs | Cap-ND18-St-SP15-100 |


Fig 1. ChroZen GC/FID with ChroZen PAL-Headspace

## *ChroZen PAL RSI?


ChroZen PAL RSI system can be adapted or extended to provide the combined injection techniques such as static headspace injection, liquid injection, SPME (Solid Phase Micro Extraction) and ITEX (In-Tube Extraction) dynamic headspace in one instrument.

ChroZen PAL RSI autosample enables to handle up to 180 capacitiy of headspace vials while ensuring both reliablity and reproducibility. Applying smart syringe technology with ID chip, it automatically preset all of syringe parameters, ranges and usage tracking for users' convenience.

## Preparation

Sample preparation was performed according to USP <467>.

### USP <467> - Class A

Standard: USP Class 1 Residual Solvent Mix (P-no. Restek 36279)

① Take 1 mL of standard, add 9 mL of DMSO and dilute to 100mL with water.

② Take 1 mL of solution ① and dilute to 100mL with water.

③ Take 10 mL of solution ② and dilute to 100 mL with water.

④ Take 1 mL of solution ③ and add 5mL of water in a headspace vial.

### USP <467> - Class 2A

Standard: USP Residual Solvent Class 2 – Mix A (P-no. Restek 36271)

① Take 1 mL of standard and dilute to 100mL with water.

② Take 1 mL of solution ① and add 5mL of water in a headspace vial.

### USP <467> - Class 2B

Standard: USP Residual Solvent Class 2 – Mix B (P-no. Restek 36280)

① Take 1 mL of standard and dilute to 100mL with water.

② Take 1 mL of solution ① and add 5mL of water in a headspace vial.

## Method

| Static Headspace Conditions |
|---|
| Incubation time: 30min |
| Incubation Temperature: 85°C |
| Agitator Speed: 750rpm |
| Purge Time: 5s |
| Syringe Temperature: 100°C |
| Injection Flow Rate: 60mL/min |
| Injection Volume: 1mL |

**Table 1. Headspace Condition**

| GC Conditions | FID Conditions |
|---|---|
| Column: Rxi-624Sil MS (30m x 0.32 mm x 1.8 µm) | Temperature: 250°C |
| Oven temperature program:<br>40°C (20 min) → 10°C/min → 240°C (20min) | Air: 300mL/min |
| Carrier gas: He (35cm/sec) | $H_2$: 30mL/min |
| Inlet: 140°C / Capillary / Split(10:1) | |

**Table 2. GC/FID Condition**

## Result

According to USP <467>, the analysis of residual solvents must meet the following system suitability requirements.

The signal-to-noise ratio of 5 residual solvents in Class 1 must be not less than 3 and 1,1,1-trichloroethane's one in the Class 1 should be not less than 5.

The resolution of acetonitrile and methylene chloride in Class 2A must be not less than 1. There is no system suitability requirement for Class mixture 2B.

### USP<467> - Class 1

As a result of the analysis of Class 1 residual solvent mixture, all compounds in Class 1 mixture had the S/N higher than 3 and 1,1,1-trichloroethane's S/N was higher than 5, which are satisfied with the requirements [Fig.2]. In particular, Carbon Tetrachloride, which has the lowest response in FID, had the S/N to 5.54 and this satisfies all requirement.

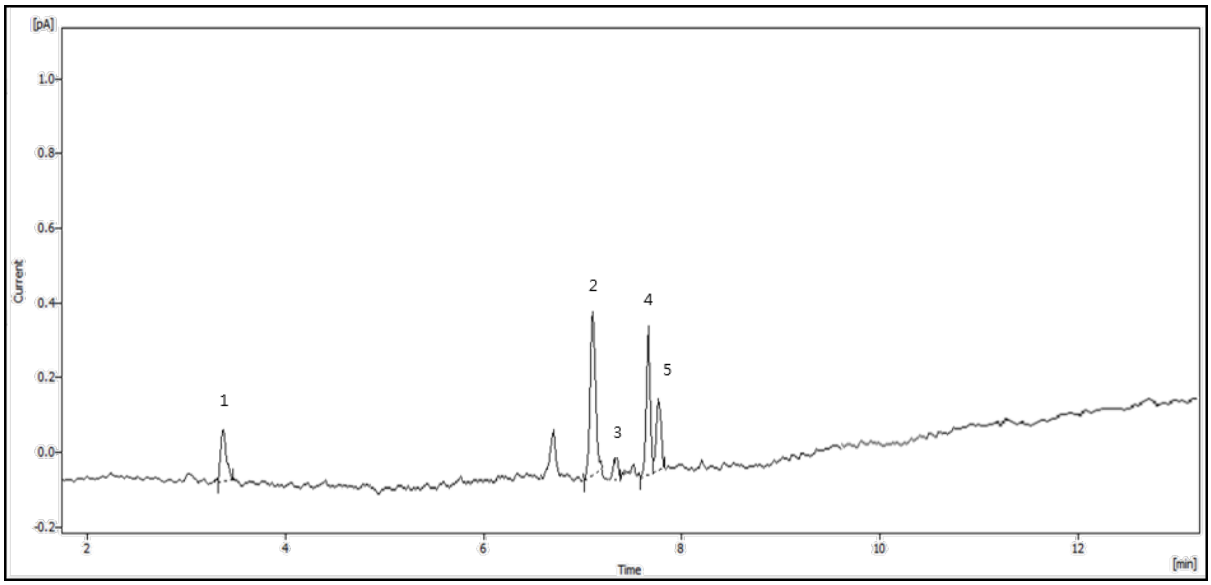


**Fig 2. Class1 Chromatogram** [1. 1,1-Dichloroethene, 2. 1,1,1-Trichloroethane, 3. Carbon Tetrachloride, 4. Benzene, 5. 1,2-Dichloroethane

## USP<467> - Class 2A, 2B

Class 2 is classified into 3 types. (2A, 2B, 2C) and USP 467 describes the methods for 2A and 2B only. [Fig 3] shows the analysis result for residual solvents in Class 2A and 2B. The resolution of Acetonitrile and Methylene chloride was 2.48, which sufficiently satisfies the requirement (not less than 1).

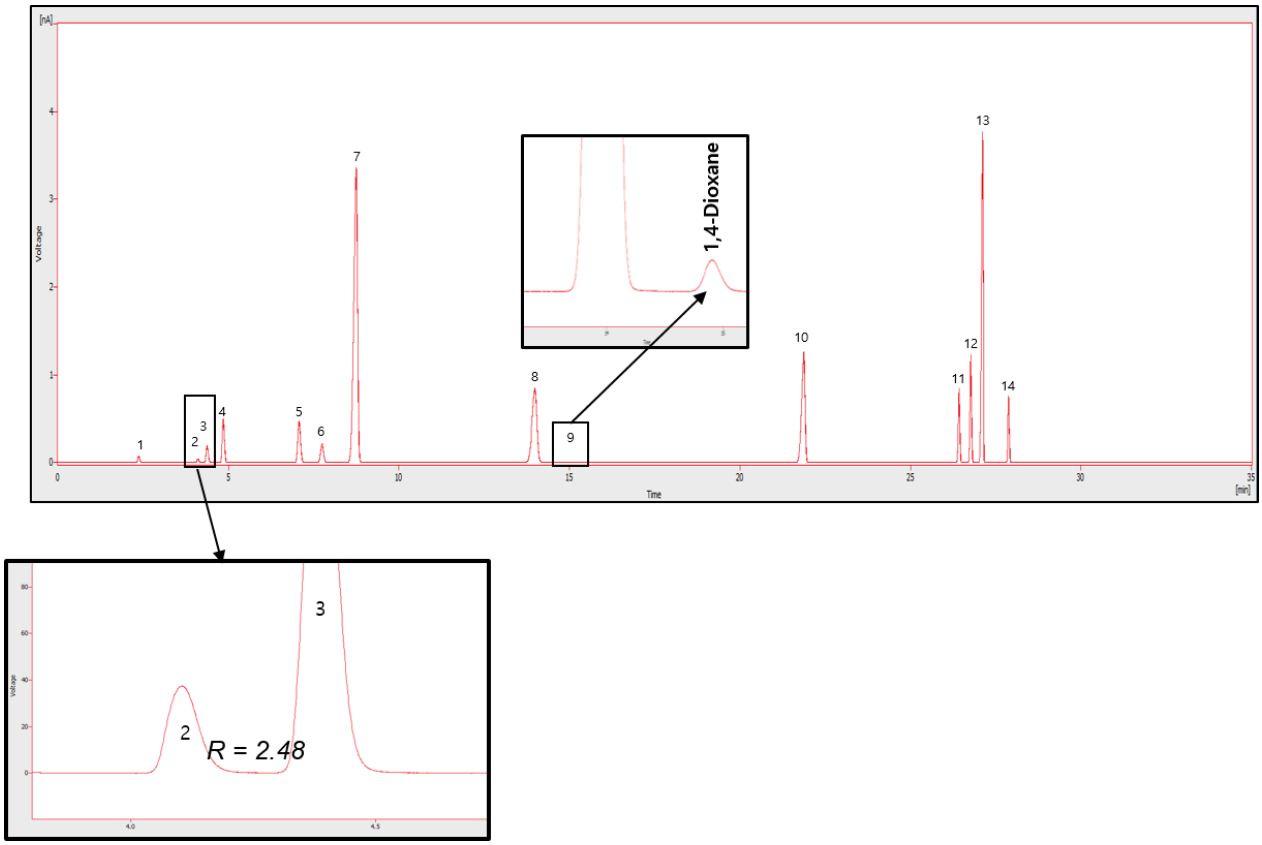


**Fig 3. Class 2A Chromatogram** [1. Methanol, 2. Acetonitrile, 3 Methylene Chloride, 4. Trans-1,2-Dichloroethene, 5. Cis-1,2-Dichloroethene, 6. Tetrahydrofuran, 7. Cyclohexane, 8. Methylcyclohexane, 9. 1,4-Dioxane, 10. Toluene, 11. Chlorobenzene, 12. Ethylbenzene, 13. m,p-Xylene, 14. O-Xylene

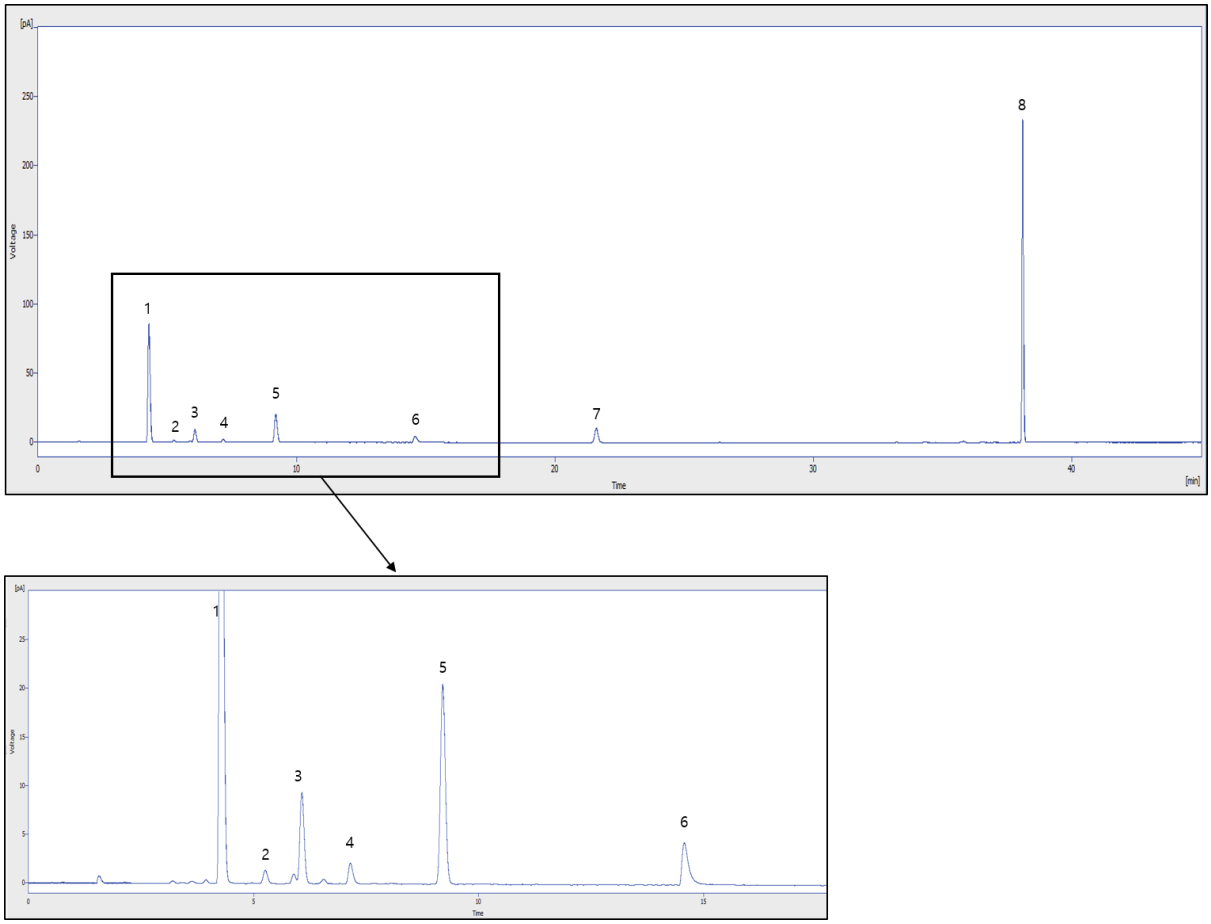


**Fig 4. Class2B Chromatogram** [1. Hexane, 2. Nitromethane, 3. Chloroform,
4. 1,2-Dimethoxyethane, 5. Trichloroethene, 6. Pyridine, 7. Methylbutylketone, 8. Tetraline

## Conclusion

In this study, the determination of residual solvents (Class 1 & 2) in pharmaceutical products by ChroZen GC/FID with Headspace was conducted according to the method (Procedure A) specified in USP 467.

All of 5 compounds in Class 1 mixture had the S/N higher than 3 and 1,1,1-trichloroethane's S/N was higher than 5. Moreover, the resolution of acetonitrile and methylene chloride was 2.48, which proves all are satisfied with the requirements.

As the results, ChroZen GC/FID with ChroZen PAL RSI Headspace is the right system for analysis of residual solvents while providing the system suitability and reliability according to USP 467.

## Reference

- United States Pharmacopeia, Residual Solvents Test <467>

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