APPLICATION NOTE

Analysis of Residual Solvents in Pharmaceuticals by Headspace-FID

AN178v1; March 2025, SCION Instruments

Introduction

Solvents are widely used during the synthesis of many pharmaceutical products. It is not always possible to remove all solvents from the final product, hence it is important that all products are tested for residual solvents. For health and safety all pharmaceutical products should be ideally free of residual solvents or at least the amount of solvents must be within the accepted limits.

The USP <467>method describes the procedure for the assay and also classifies the solvents into three categories.[1]

- Class 1: Solvents with unacceptable toxicity
- Class 2: Solvents of moderate toxicity
- Class 3: Solvents of low toxicity

Not all solvents are included within the three categories and therefore screening of additional solvents as per the manufacturing process may also be required for some pharmaceuticals.

The USP <467> method states the analysis of the solvents is separated into three procedures: Procedure A, B and C.[1] Procedure A is used to identify the analytes and conduct a concentration limit test. Procedure B is to confirm the analytes seen in Procedure A if above limit. Procedure C is used if concentrations are above limits to quantify the concentration of residual solvents in the sample. Results from Procedure A or B can be used for this calculation, dependent on which procedure gives the best resolution of the required solvents.

Headspace analysis negates the need for complex sample preparation and is a fast and simple way of analysing complex solid and liquid matrices.

In this application note we will validate a method for residual solvent analysis using the SCION Versa static headspace analyser in addition to the SCION 8300 GC and FID.

Experimental

Class 1, 2A and 2B residual solvents stocks, standards and system suitability solutions were prepared in accordance to the method USP<467> "water soluble articles".[1] The solutions were prepared using residual solvents class 1, 2A and 2B mix standards.

For the test stock and solution the article chosen was own brand supermarket paracetamol. The test solution was made in line with USP<467> "water insoluble articles".[1]

The instrument parameters for both the GC and headspace (Versa) sampler can be found in Table 1.

Table 1 Instrument parameters

Part	Settings
Autosampler (Headspace)	Versa: Valve oven 90 °C Transfer line temp. 105 °C Platen temp. 80 °C Sample equil. time 45 min Mix @ medium for 2 min Pressurize @ 9 psig for 2 min Loop fill pressure: 7 psig Loop fill time: 2 min Loop size: 1 mL Inject time: 0.5 min
Injector	260 °C Split ratio 5:1
Column	SCION-624MS 30 m x 0.25 mm x 1.4 µm (Procedure A) SCION-WAXMS 30 m x 0.25 mm x 0.25 µm (Procedure B)
Carrier Gas	Helium 1.5 mL/min
Oven Program	40°C (hold 20 min), 10°C/min to 240°C (hold 20 min)
Detector	FID (ceramic jet) 275°C Air : 300 mL/min Hydrogen : 30 mL/min Make up (N_2): 25 mL/min
Run Time	60 min
Software	Compass CDS Versa Teklink

Procedure A is used to identify the analytes and investigate the quantities of each analyte in the sample on a 624 phase column. For this procedure a SCION-624MS column was used. Procedure B is then run using a WAX phase column to confirm the analytes seen in Procedure A. For Procedure B a SCION-WAXMS column was used. Separate sample vials were used for Procedure A and B. Procedure C identified which phase column gave the best separation and using that data to quantify the concentration of residual solvents in the sample. See our complimentary chromatography guide.

Results

The instrument method stated gave excellent specificity. All compounds resolved as expected and exhibited good peak shape.

Tables 2, 3 and 4 show the system precision for all the compounds present in the residual solvent mixes for classes 1, 2A and 2B for Procedure A. The results show all compounds demonstrate good repeatability with the majority of compounds showing RSD% <5% and all <10%. RSD's below 10% is industry standard when it is not defined in the reference method.

Table 2 System precision results for Class 1 residual solvents

Class 1	RSD(%)
1,1-Dichloroethene	1.15
1,1,1-Trichloroethane	2.74
Carbon tetrachloride	2.56
Benzene	4.38
1,2-Dichloroethane	5.46

Table 3 System precision results for Class 2A residual solvents

Class 2A	RSD(%)
Methanol	0.81
Acetonitrile	0.93
Methylene chloride	1.38
trans-1,2-Dichloroethene	1.38
cis-1,2-Dichloroethene	1.44
Tetrahydrofuran	0.62
Cyclohexane	4.51
Methylcyclohexane	6.61
1,4-Dioxane	2.22
Methylisobutylketone	0.66
Toluene	1.13
Chlorobenzene	1.01
Ethylbenzene	1.24
m-xylene & p-xylene	1.25
o-xylene	1.48

Table 4 System precision results for Class 2B residual solvents

Class 2B	RSD(%)
Hexane	0.78
Nitromethane	2.12
Chloroform	0.88
1,2-Dimethoxyethane	1.42
Trichloroethylene	2.04
Pyridine	1.35
Methylbutylketone	1.73
Tetrain	0.47

Table 5 Resolution for Procedure A and Procedure B

Procedure	Resolution Factor
A	1.51
B	2.06

As stated in the USP <467> method in Procedure A the resolution between acetonitrile and methylene chloride in Class 2 Mixture A standard solution should not be less than 1.0. Resolution above 1.0 was achieved with a resolution factor of 1.51 as seen in Table 5. In Procedure B the resolution between cis-1,2-Dichloroethene and acetonitrile was found to be 2.06 which is greater than the required resolution 1.0.

Figures 1-5 show example chromatograms from the analysis of residual solvents classes 1, 2A and 2B for Procedure A on a SCION-624MS column. It was determined that it was possible to reach the concentration limit stated in <USP 467> for classes 1, 2A and 2B.

Figure 6 shows example chromatograms overlaid of class 1 residual solvents, the solvents which must be avoided, and the chosen article pharmaceutical, supermarket own brand paracetamol. The results showed that there was no residual solvents found above the concentration limit for classes 1, 2A or 2B in Procedure A.

It was expected that there would be no residual solvents found above the concentration limit for classes 1, 2A or 2B due to purchasing a paracetamol that is readily available to the consumer.

Figures 7-11 illustrate example chromatograms from Procedure B where residual solvents classes 1, 2A and 2B were analysed on a SCION-WAXMS column. Procedure B was used to confirm the analytes seen in Procedure A but it was determined the SCION-624MS column gave better resolution across all three classes compared to the WAX phase column.

From the analysis conducted, it was observed that the SCION-624MS column gave the least amount of coelution and hence overall gave the best peak resolution. If it was found that concentration limits of residual solvents in Procedure A on the 624 phase column were above the limits stated in USP <467> then identify would be verified using Procedure B on the Wax phase column. If again concentration limits stated in USP <467> were greater or equal to those found in Procedure A then proceed to Procedure C. As per Procedure C in USP <467> the results from Procedure A would be used for quantification.

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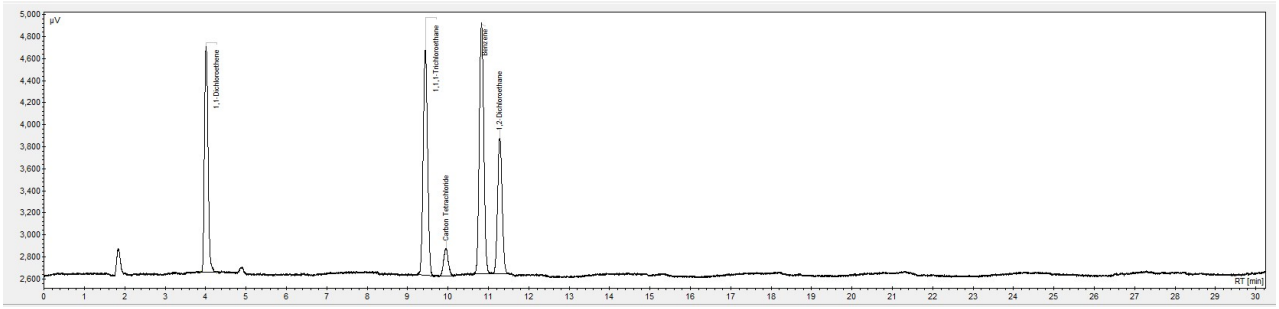

Figure 1 Example chromatogram of residual solvents class 1 mix Procedure A

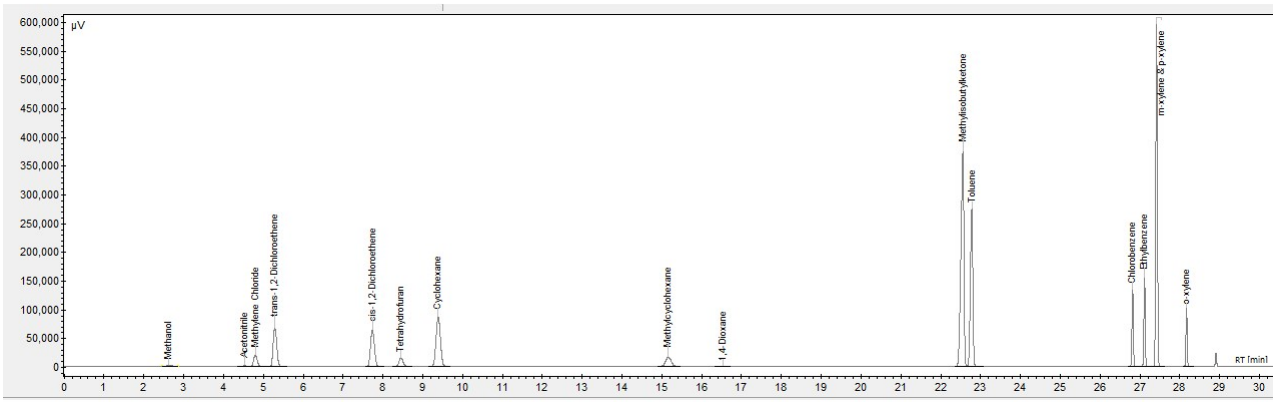

Figure 2 Example chromatogram of residual solvents class 2A mix Procedure A

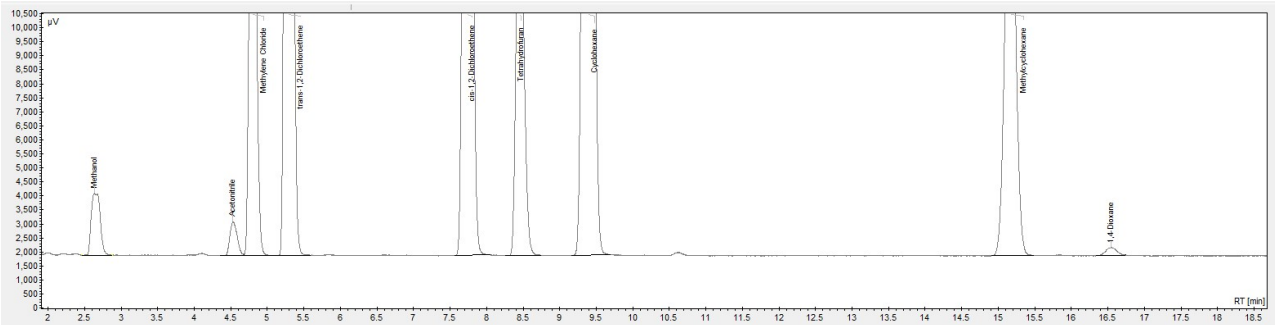

Figure 3 Example expanded chromatogram of residual solvents class 2A mix Procedure A

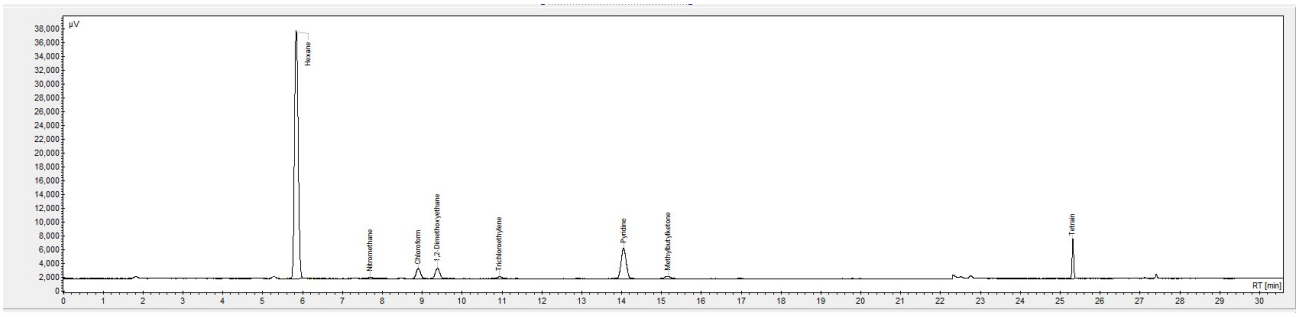

Figure 4 Example chromatogram of residual solvents class 2B mix Procedure A

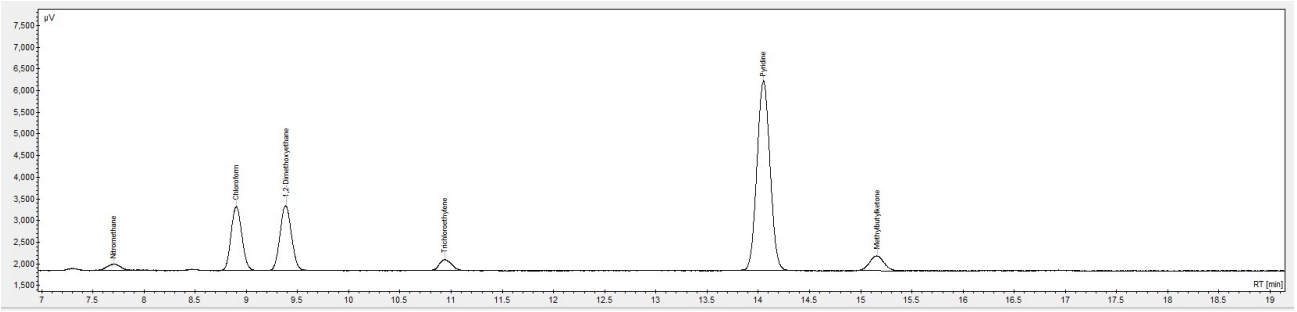

Figure 5 Example expanded chromatogram of residual solvents class 2B mix Procedure A

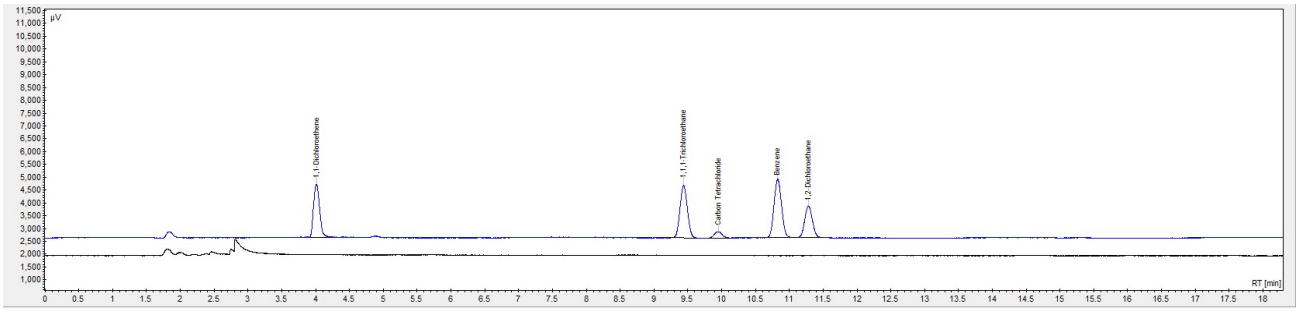

Figure 6 Example chromatogram of residual solvents class 1 mix overlaid with chosen article sample Procedure A

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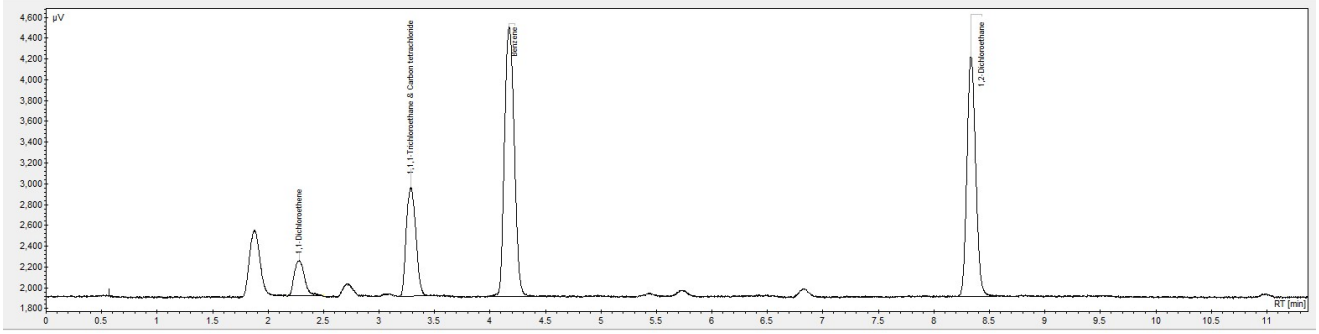

Figure 7 Example chromatogram of residual solvents class 1 mix for Procedure B

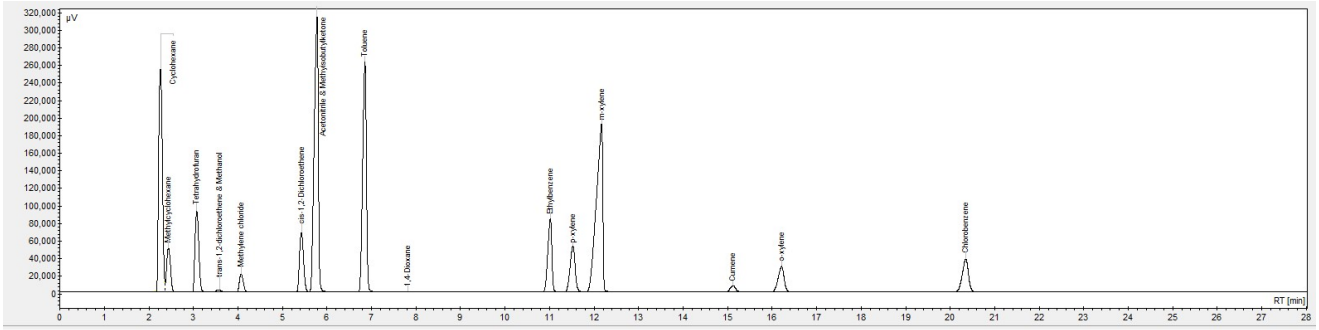

Figure 8 Example chromatogram of residual solvents class 2A mix for Procedure B

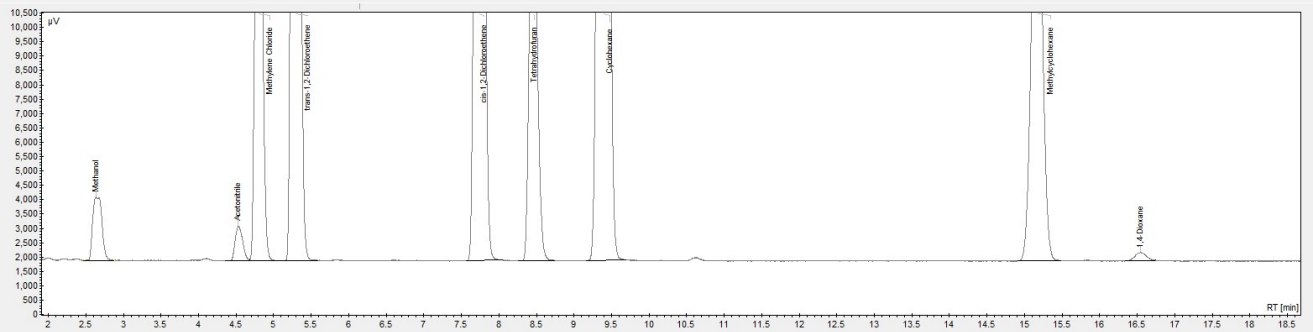

Figure 9 Example expanded chromatogram of residual solvents class 2A mix for Procedure B

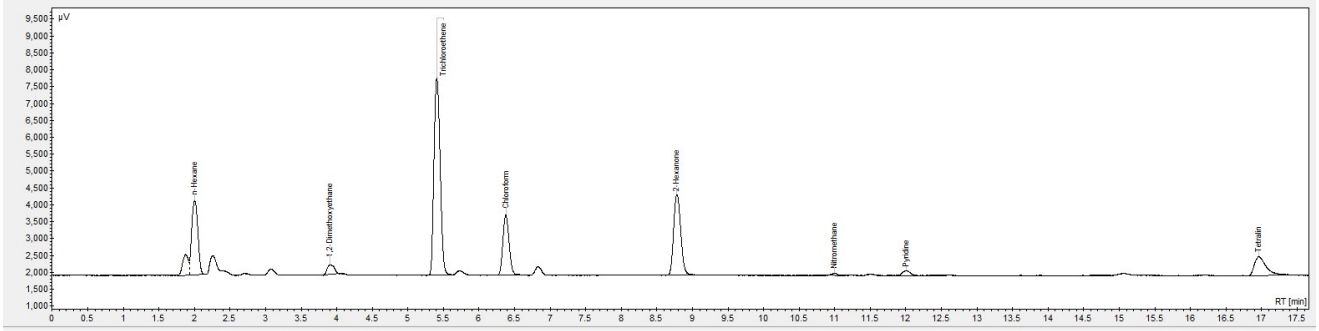

Figure 10 Example chromatogram of residual solvents class 2B mix for Procedure B

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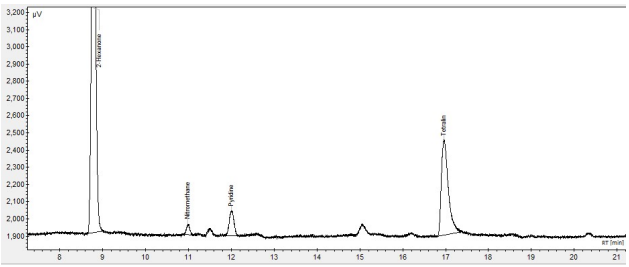

Figure 11 Example expanded chromatogram of residual solvents class 2B mix for procedure B

Conclusions

The SCION Versa static headspace analyser in addition to the SCION 8300 GC and FID was used to validate a method for residual solvent analysis for residual solvents in pharmaceuticals classes 1, 2A and 2B. All compounds across the classes mixes demonstrated the expected separation and good peak shape.

The results show all compounds demonstrate good repeatability and the concentration and resolution limits stated in USP <467> were able to be met.

As expected, the supermarket own brand paracetamol which was purchased for analysis against residual solvents classes 1, 2A and 2B was not found to contain any residual solvents above the concentration limits.

As stated in USP <467> if concentration limits for residual solvents were exceeded in Procedure A on the SCION-624MS column then identify of the compounds would be verified on SCION-WAXMS column as per Procedure B. If concentration limits are greater or equal to those found in Procedure A then quantification would be conducted using SCION-624MS column as per Procedure C due to the superior peak resolution observed.

SCION instruments recommends checking with local regulatory authorities to ensure all testing and reporting requirements are met, or contact the SCION applications team for assistance.

Ordering Information

Ordering Information for the 8300 GC	
Part	**Part Number**
8300-GC, with S/SL inlet and FID detector (120V)	839001701
8300-GC, with S/SL inlet and FID detector (230V)	839001702
Versa Static Headspace Vial Sampler 110 V	SC150800100
Versa Static Headspace Vial Sampler 230 V	SC150800200
Suggested Consumables	
Part	**Part Number**
15% Graphite/85% Vespel Ferrule 1/16" with 0.4 mm hole pk/10	41312148
BTO Septa 9 mm, pk/50	CR298713
20 mL Clear Glass Headspace Vial	41311008
20 mm Aluminium Crimp Cap with 20 mm Natural PTFE/White Silicone Septa 3mm Thick	41311010
SCION-624MS 30 m x 0.25 mm x 1.4 µm	SC32591
SCION-WAXMS 30 m x 0.25 mm x 0.25 µm	SC32423
Liner SCION Taper Focus Ultra	41312115

References

1. USP-NF, https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/generalChapter467Current.pdf, (accessed 06 Mar 25)

For more information, please contact:

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