



Residual Solvent  
Analysis

## Application Notes #283030

# Determination of Class I USP Residual Solvents and TICs in Dietary Supplements and Pharmaceutical Products by GC/MS

Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are consumed or produced in the manufacture of drug products. It is known that these residual solvents are not completely removed by practical manufacturing techniques. The United States Pharmacopeia (USP) <467> specifies the gas chromatographic (GC) conditions for the analysis of these organic volatile impurities. Static headspace analysis coupled with gas chromatography mass spectrometry (GC/MS) is the ideal technique for the analysis, because target and unknown compounds can be analysed simultaneously with complete confidence in the identification and quantification of the results. The new Scion automated static headspace auto sampler, the SHS-40, is combined with the SCION SQ mass spectrometer for the analysis of Class I residual solvents in pharmaceutical and dietary supplement products. Non-target compounds are also determined by automated library search.

### Introduction

Class 1 residual solvents should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents (1). Table 1 provides a list of the compounds and the concentration limits, along with the general concern for each.

**Table 1. Class I Residual Solvents.**

Compound	Limit (ppm)	Hazard
Benzene	2	Carcinogen
Carbon Tetrachloride	4	Toxic Env Hazard
1,2-Dichloroethane	5	Toxic Env Hazard
1,1-Dichloroethene	8	Toxic Env Hazard
1,1,1-Trichloroethane	1500	Toxic Env Hazard

The sample is typically analysed by headspace coupled with gas chromatography (non-MS detectors such as FID). The SCION SQ can be operated in a single ion monitoring (SIM) mode and SCAN mode simultaneously, which provides very low limits of quantitation for the target residuals along with identification of other compounds that may be present in the sample.

A unique feature of SCION is the ability to set up methods rapidly using Compound Based Scanning (CBS). CBS makes use of libraries that contain all scan and retention time information for a given set of compounds that are loaded directly into an acquisition method and data handling compound table in one easy step. Figure 1 shows the Class I Residual Solvents and a full scan segment in a library that are easily loaded into the method. Figure 2 is a graph of the compound acquisition windows that have been automatically created by CBS for optimal sensitivity and quantitative analysis.

**Figure 1. A CBS Library of USP Class I Residual Solvents.**

Name	CAS No.	MW	Boiling Point	Melting Point	Density	Refractive Index
Acetone	67-64-1	58.08	56.2	-17.7	0.791	1.36
Ethyl Acetate	99-07-8	88.10	77.1	-84.3	0.902	1.37
Toluene	108-88-3	92.14	110.6	-93.6	0.867	1.49
Methanol	67-58-0	32.04	64.7	-97.7	0.791	1.33
Diethyl Ether	109-87-1	74.12	34.6	-116.3	0.714	1.35
Propyl Acetate	109-62-9	102.13	101.1	-93.6	0.886	1.39
Butyl Acetate	123-86-4	116.16	126.1	-79.3	0.883	1.41
Hexane	110-52-3	86.17	68.7	-95.3	0.659	1.39
Heptane	142-92-1	98.19	98.4	-94.3	0.684	1.41
Octane	142-92-1	114.23	125.7	-89.3	0.703	1.43
Nonane	111-84-1	128.26	150.8	-85.5	0.720	1.45
Decane	142-92-1	142.29	176.1	-81.8	0.730	1.47

**Figure 2. Optimized Compound acquisition summary with simultaneous Full Scan and SIMs.**



## Experimental

A vitamin dietary supplement, a common pain reliever and an allergy medication were prepared for static headspace analysis by dissolving 250mg of the finished product in 25mL of water. Five milliliters (5mL) was transferred to a 20mL headspace vial with a screw-cap teflon-faced septum. Two grams of sodium sulfate anhydrous was added to each vial, along with 1.0mL deionized reagent water.

Standards containing the Class I USP residual solvents were prepared such that all compounds were at the same final concentrations of 0.1, 1.0, and 10ppm. The 0.1 and 1.0ppm standards are well below the individual compound required concentration limits shown in Table 1. A volume of 1.0mL was transferred to 5mL deionized reagent water, along with 2g sodium sulfate anhydrous.

The samples were placed on the Scion SHS-40 headspace auto sampler, with the conditions listed in Table 2.

**Figure 3. Scion SHS-40 Headspace Autosampler with SCION GC/MS.**



**Table 2. SHS-40 Sampling Conditions.**

Parameter	Set Point
Oven Temp	85°C
Valve/Loop Temp	160°C
Transfer line Temp	125°C
Pressure	500psi
Loop Volume	1mL
PC (incubation) Time	30 min
GC/MS Run Time	20 min
Shake option	ON

The SCION GC/MS column, oven program, and injector conditions:

Column: BR-624ms, 20M x 0.18mm x 1.0um  
 Injector: BR-1079, PTV injector with 3.4mm single goose-neck open split liner set at 200°C  
 Injector split ratio: 1:20  
 Column flow: 1mL/min.  
 Oven program: Initial 35°C hold 2 min; program to 170°C at 10°C/min; hold 0; program to 250°C at 50°C/min, hold 1 min, (total run time 17.9 min.)

**Table 3. Synchronous SIM/SCAN parameters set up using CBS for Class 1 USP Residual Solvents.**

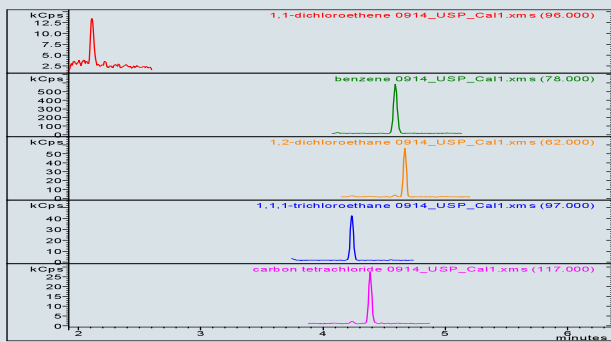
Compound Name	Retention Time (RT)	RT Window	Scan Mode, Ions monitored	Dwell Time (ms)
1,1-Dichloroethene	2.10	1.0	SIM, 61, 96, 98	49
1,1,1-Trichloroethane	4.23	1.0	SIM, 97, 99	49
Carbon tetrachloride	4.38	1.0	SIM, 117, 119	49
Benzene	4.59	1.0	SIM, 77, 78	49
1,2-Dichloroethane	4.67	1.0	SIM, 62, 64	49
Full Scan	NA	2.0-17.9	Full (m/z 35-300)	300

## Results

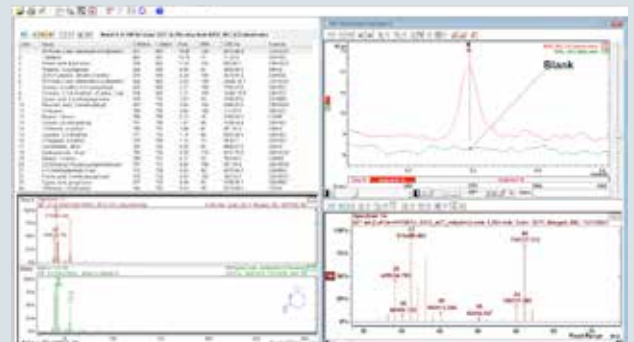
The instrument in the SIM/Scan mode provided excellent sensitivity as seen in Figure 4. All of the compounds are easily detected at the 0.1ppm level, with excellent peak shape due to the 1:20 split. Since qualifier ions are also monitored, unambiguous results are obtained. The correlation coefficient (r(2)) for all curves were greater than 0.999. An example calibration curve for 1,1,1-trichloroethane is shown in Figure 5.

None of the Class 1 Residual Solvents were detected in any of the test samples. However, other compounds showed up in the full scan data. The Scion MSWS 8 software is capable of automated peak detection and library searching of unknown peaks. The tentatively identified compounds (TICs) can be reviewed to identify potential problems that may be occurring in the manufacturing process. The pain reliever had a good match for several compounds (reverse fit match greater than 800 for top 10 hits). The compound was not detected in the blank or control samples (Figure 6).

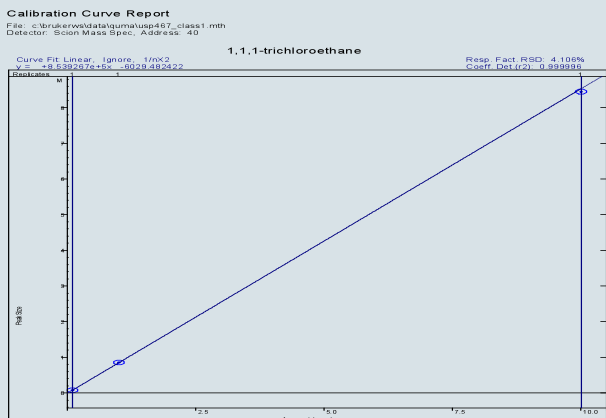
**Figure 4. Measurement of USP Class I Residual Solvents at 0.1 ppm.**



**Figure 6. TIC detected in pain reliever.**

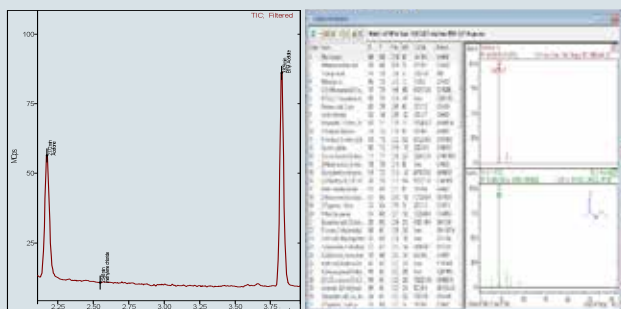


**Figure 5. Calibration curve, from 0.1 to 10 ppm of 1,1,1-trichloroethane.**



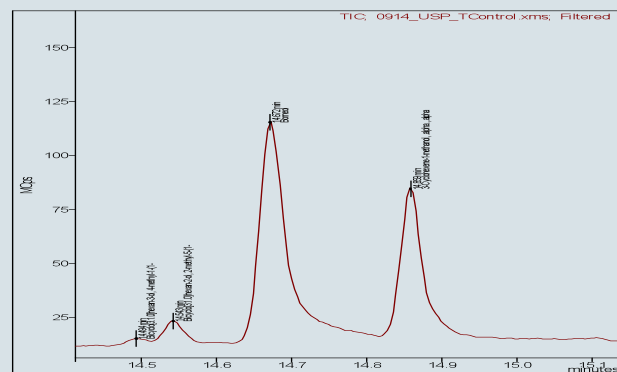
These are part of a list that includes solvents that are not known as human health hazards at levels normally accepted in pharmaceuticals. The allergy medication had relatively high concentrations of ethyl acetate and acetone detected in the sample as indicated in Figure 7. These are Class 3 Residual solvents. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies (2).

**Figure 7. Residual Class 3 solvents, acetone and ethyl acetate, found as TICs in the allergy medication.**



The multi-vitamin (also advertised as having weight-control benefits) had some peaks eluting near the end of the chromatographic run. Borneol and other terpenes were detected in the sample.

**Figure 8. Multi-vitamin/weight loss control dietary supplement with TIC borneol detection.**



## Conclusion

The Scion SHS-40 headspace auto sampler coupled with the SCION GC/MS provided excellent detection limits and quantitative data for the Class I USP Residual Solvents. Compound Based Scanning (CBS) makes it easy to set up optimized acquisition and data handling methods directly from compound libraries with a single click. None of the target residual solvents were detected in the three products studied, however other TICs were found by examining the SCAN data. This additional data can alert the quality control manager of potential contamination in the manufacturing process, or be used to evaluate other non-regulated compounds present in the product.

## References

(1) and (2): Chemical Tests: General Chapter (USP) <467> Residual Solvents, Organic Volatile Impurities, July 2007

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