Application Note

Pharmaceuticals

USP<467> residual solvents

Applying the Agilent 5977A MSD with the Agilent 7697A headspace sampler and Agilent 7890B GC

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Abstract

The Agilent 7697A headspace sampler coupled to an Agilent 5977 Series GC/MSD System was used for the analysis of USP <467> residual solvents at their limit concentration in aqueous solution according to procedure A of the method. Scan data gave repeatability better than 2.5 % RSD for Class 1, Class 2A, and Class 2B solvents. The multimode inlet (MMI) with an Ultra Inert 1-mm id liner was used for sample introduction from the fused silica headspace transfer line. Several tunes were investigated including Atune and Etune for data acquisition with source and quadrupole temperatures of 250 and 200 °C, respectively. Agilent MassHunter Quant software was used for data analysis.

Introduction

Quality assurance (QA) labs routinely use United States Pharmacopeia (USP) Method <467> for the analysis of residual solvents[1]. This method is used worldwide for quality control. It is harmonized with Guidance for Industry ICH Q3C Impurities.

Residual solvents in pharmaceuticals may remain from the manufacturing process of the active pharmaceutical ingredients (APIs) or final product. Residual solvents do not provide a therapeutic benefit, and should be removed when possible. Monitoring and control of the levels of residual solvents are also done for safety, effect on crystalline form, solubility, bio-availability, and stability. All drug substances, excipients, and products must be monitored.

The USP <467> guidelines were followed[1]. To take advantage of the advance features of the Agilent 7697A headspace sampler, modification and optimization of the headspace parameters were made. Analysis methodologies that deviate from the USP monograph can be used; however, validation and comparison to the original USP procedures may be required. Each class of solvents was run separately for clarity.

USP <467> specifies the following three procedures for Class 1 and Class 2 residual solvents:

- **Procedure A:** Identification and limit test
- **Procedure B:** Confirmatory test
- **Procedure C:** Quantitative test

Procedure A uses a G43 phase (Agilent 624 columns, VF-624ms or DB-624), and Procedure B uses a G16 phase (HP-INNOWax). In general, analytes that coelute on one of these phases do not coelute on the other. Since the primary objective of this Application Note centers on evaluating analytical sensitivity and repeatability, only the VF-624ms column was used. Other configurations using dual FIDs (624 and INNOWax columns) or FID/MSD are possible, and have previously been described[2,3,4,5].

The headspace-based method has historically suffered from poor repeatability when analyzing solvents at or below their USP <467> limit concentrations. Use of advanced pneumatics, excellent thermal zone control, and precise timing translates into better repeatability and precision for residual solvent analysis. Features of the Agilent 5977A Series GC/MSD System, including an inert extractor source also contribute to improved repeatability.

GC-headspace-MSD systems can offer additional capabilities for residual solvent analysis, especially when unknowns are encountered. Using SIM, coelution problems are overcome and better analytical sensitivity can be achieved.

Experimental

This Application Note used USP Method <467> Procedure A to investigate the performance of the 5977 Series GC/MSD System with the 7890B-7697A. The Agilent 7890B GC was configured with a multimode inlet (MMI). A 1-mm id deactivated straight liner (p/n 5190-4047) was used.

Class 1, Class 2A, and Class 2B residual solvents were prepared at their limit concentrations in purified water. Clean organic-free water is important for good standard preparation. There were 250-mL solutions of each class prepared at their final concentrations, then 6 mL was transferred into 20-mL vials using an auto pipette. Only PTFE-lined septa were used. Salt was not added to the solution. Agilent part numbers for the residual solvent standards are:

Class 1: p/n 5190-0490

Class 2A: p/n 5190-0492

Class 2B: p/n 5190-0513

The Agilent 7697A headspace sampler was connected to the inlet using 0.53-mm id deactivated fused silica tubing. Interface to the MMI was through the septum. A 30 m, 0.25-mm id VF-624ms column was used for this work, as it represents a good compromise between resolution, speed, capacity, and ease-of-use.

Vial pressure was controlled from a pneumatic control module (PCM) in the 7697A headspace sampler. The carrier flow was routed from the inlet EPC to the headspace sampler and back to the 7890B inlet. EPC-controlled sampling steps give the user control over all aspects of headspace vial sampling in a concise and reproducible method with minimal carryover. Barometric pressure compensation is also implemented in the EPC modules. Parameters can be set from the 7697A headspace sampler keyboard or integrated headspace control software. Figure 1 shows the headspace vial sampling pane from the MSD ChemStation.

The use of controlled venting in the 7697A headspace sampler allows the user flexibility over the final vial pressure when filling the sample loop. This control leads to better repeatability and, depending on the analyte k (partition coefficient) value, it can also enhance sensitivity[6]. Three modes of vial pressurization are possible in the 7697A headspace sampler:

- Flow limited to pressure
- *To pressure*, controlled at flow of 200 mL/min
- Fixed volume

All experiments used the *to pressure* mode. Figure 1 shows a MSD ChemStation pane for setting the vial sampling parameters. Note that HS vial pressure ramps from 15 to 10 psi for headspace sampling.

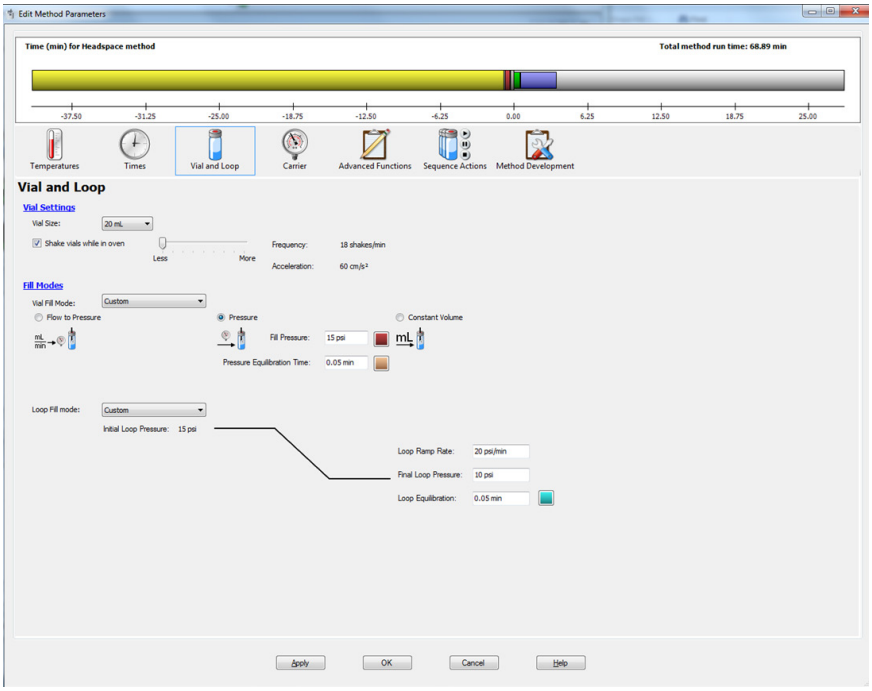

Figure 1. Parameters are shown for 20-mL vials, where the HS vial is pressurized to 15 psi, and vented to 10 psi at a rate of 20 psi/min.

A moisture trap designed to reduce condensation is plumbed in the vent line and is purged between runs. The headspace sample loop is 1.0 mL. Helium is used for carrier and vial pressurization. Table 1 gives the application-specific parameters.

Agilent MassHunter Software

The 5977 Series GC/MSD system introduction includes the ability to use Agilent MassHunter (MH) software similar to that on the Agilent 7000B GC/MS/MS. The data acquisition has been improved, especially in the ease of setting up SIM tables. SIM, scan, and temperature parameters are on a single screen for quick review. Current MSD ChemStation acquisition methods can be imported and used directly in MH.

Data analysis is accomplished using either MH Qualitative Analyses (Qual) or MH Quantitative Analysis (Quant). This Application Note used Qual for the chromatogram displays. Quant was used for compound integration, and subsequent RSD calculations were done in Excel. Current MSD ChemStation quant databases (calibration tables) can easily be converted for use in MH Quant with the included Converter.

Using MH Qual and Quant is not required. The 5977 Series GC/MSD system acquisition software automatically saves data in both MH format and classical MSD ChemStation format. Laboratories have a choice in data analysis packages.

This work used the following software versions:

- MSD ChemStation B.07.00 acquisition
- MassHunter B.05.01 Quant
- Headspace control software B.01.04

Table 1. System parameters for the analysis of residual solvents.

Parameter	Value
Gas chromatograph	Agilent 7890B GC
Injection port	Multimode Inlet
Liner	1-mm id Ultra Inert (p/n 5190-4047)
Inlet temperature	140 °C
Inlet flow	Constant flow, 1.3 mL/min
Split ratios	20:1, 100:1
Oven program	40 °C (5 minutes) to 240 °C (2 minutes) at 18 °C/min
Column	VF-624ms, 30 m × 0.25 mm, 1.4 µm
MSD	Agilent 5977A Series GC/MSD System
Transfer line	190 °C
MS source	250 °C
MS Quad	200 °C
Tune	etune, atune, and bfb tunes used
Scan	29 to 150 amu, 10.3 scans/sec
Gain factor	1.00
Headspace	Agilent 7697A Headspace Sampler
Vial pressurization gas	Helium
Loop size	1.0 mL
Vial standby flow	20 mL/min
Transfer line	0.53-mm deactivated fused silica
HS Oven temperature	85 °C
HS Loop temperature	85 °C
HS Transfer line temperature	100 °C
Vials	20 mL, PTFE/silicone septa
Vial shaking	Level 1
Vial fill mode	To pressure
Vial fill pressure	15 psi
Loop fill mode	custom
Loop ramp rate	20 psi/min
Loop final pressure	10 psi
Loop equilibration time	0.05 minutes
Carrier control mode	GC carrier control
Vent after extraction	ON
Post injection purge	100 mL/min for 3 minutes

Results and discussion

Figure 2 shows the TIC for the Class1 residual solvents at their limit concentrations prepared in pure water. Class 1 solvents benzene and 1,2-dichloroethane are baseline separated on the VF-624ms column.

Table 2 shows that scan RSDs are reported for all classes, and SIM RSDs for Class 2A. Most RSDs are below 2.5 %. Those with higher values generally have low k's. Sample preparation variability can have a larger impact on low k solvents. Other solvent systems such as dimethyl sulfoxide (DMSO), dimethyl acetamide (DMAC), 1,3-dimethyl-2-imidazolinone (DMI), or mixed, such as DMSO/water, will change the response. RSDs should be equal if not better than those shown in this work using an aqueous diluent.

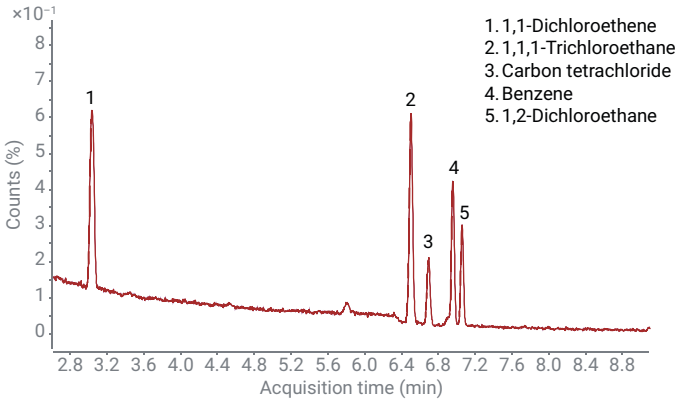

Figure 2. TIC for the Class 1 residual solvents at their limit concentrations prepared in pure water.

Table 2. Residual solvent Class1, Class 2A, and Class 2B repeatability. Scan data are shown for all classes, and SIM data for Class 2A. Prepared at limit concentrations in aqueous diluent.

Compound	USP limit (ppm)	Scan RSD (%)	SIM RSD (%)
Class 1 (n = 8)			
1,1-Dichloroethene	8	0.9	
1,1,1-Trichloroethane	1,500	1.9	
Carbon tetrachloride	4	1.5	
Benzene	2	0.7	
1,2-Dichloroethane	5	0.9	
Class 2A (n = 10)			
Methanol	3,000	2.8	2.4
Acetonitrile	410	3.3	2.3
Dichloromethane	600	2.5	2.2
trans-1,2-Dicloroethene	1,870	2.4	2.2
cis-1,2-Dichloroethene	1,870	2.1	2.1
Tetrahyrofuran	720	3.0	2.2
Cyclohexene	3,880	2.7	1.3
Methylcyclohexane	1,180	4.3	1.6
1,4-Dioxane	380	2.6	2.3
Toluene	890	0.7	2.0
Chlorobenzene	360	1.9	2.1
Ethylbenzene	2,170	1.9	2.1
m-Xylene, *p*-Xylene	2,170	2.1	1.8
o-Xylene	2,170	2.1	1.8
Class 2B (n = 9)			
Hexane	290	3.2	
Nitromethane	50	3.8	
Chloroform	60	2.5	
1,2-Dimethoxyethane	100	2.7	
Trichloroethene	80	2.5	
Pyridine	200	3.9	
2-Hexanone	50	2.4	
Tetralin	100	2.5	

Figure 3 shows a representative TIC for Class 2A solvents. Figure 4 shows a zoom-in on the chromatogram to illustrate the small peaks.

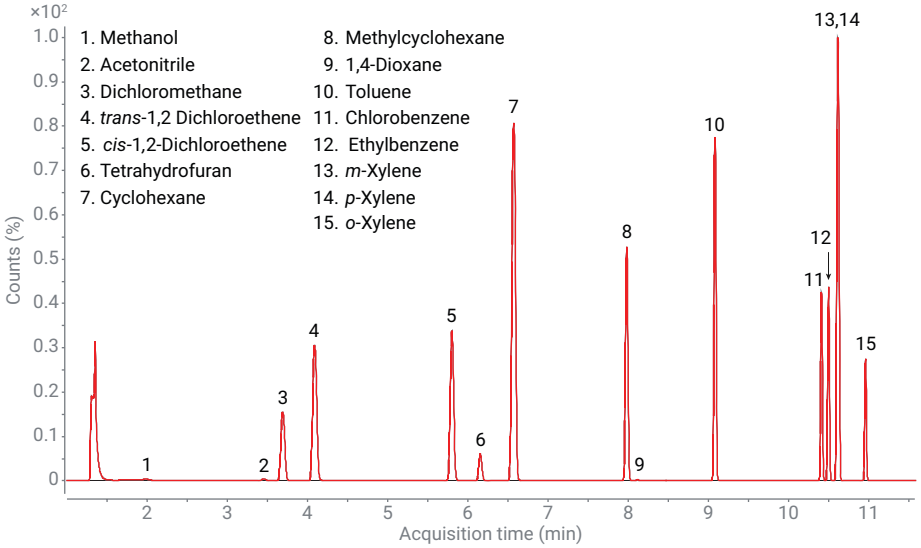

Figure 3. Representative TIC for Class 2A solvents.

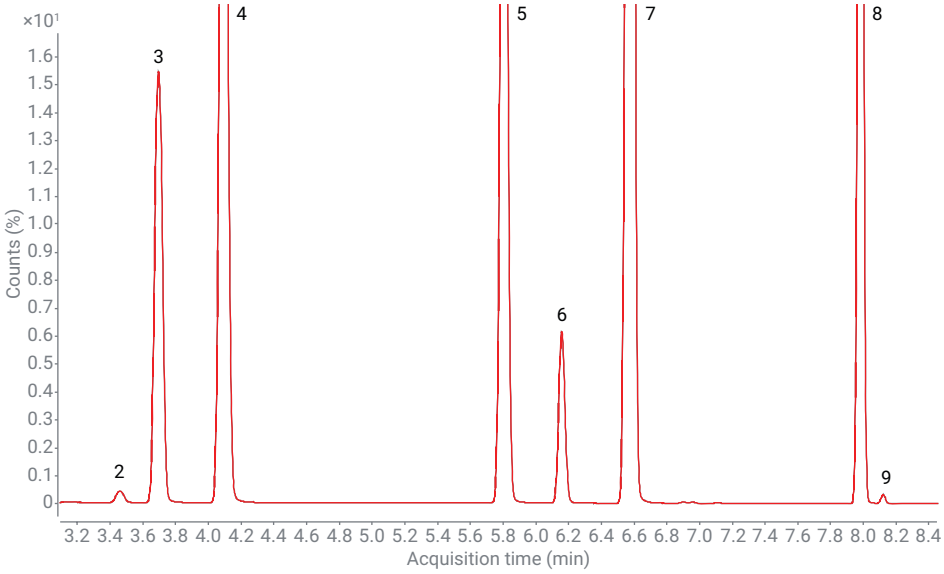

Figure 4. A zoom-in on the chromatogram to illustrate compounds with low response: acetonitrile and 1,4-dioxane. See Figure 3 for peak numbers.

Figure 5 and Table 3 respectively, show a SIM chromatogram and SIM ions used. This analysis used a split ratio of 100 to 1. The faster sweep of the liner leads to greatly improved methanol peak symmetry. Even at this high split ratio, signal-to-noise (S/N) is excellent.

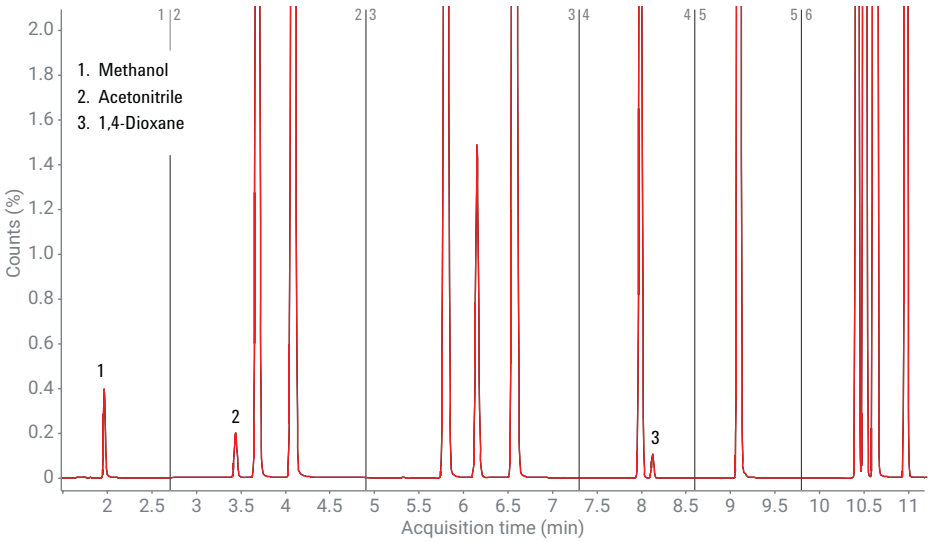

Figure 5. Class 2A SIM chromatogram and SIM group time brackets used.

Table 3. SIM groups for Class 2A solvents.

Group	Compound	SIM ions
1	Methanol	31,29
2	Acetonitrile Dichloromethane *trans*-1,2-Dicloroethene *cis*-1,2-Dichloroethene	39,41,84,86,96,98
3	Tetrahyrofuran Cyclohexene Methylcyclohexane	56,71,72,84,96,98
4	1,4-Dioxane	58,83,88,98
5	Toluene	91,92
6	Chlorobenzene Ethylbenzene *m*-Xylene, *p*-Xylene, *o*-Xylene	91,106,112,114

Figure 6 shows the SCAN/SIM setup pane (Class 2A) from MSD ChemStation acquisition. Figure 7 shows a typical SIM run for Class 2B solvents. The split ratio is 20:1. Good S/N is seen for nitromethane. Pyridine, always a difficult solvent due to its polarity, shows minimal peak tailing on the VF-624 ms column. Table 4 gives the SIM parameters used, and Figure 8 shows a setup pane from the MSD ChemStation.

Coelutions can occur on the 624 phase when all three classes of solvents are considered. This usually is dealt with in FID systems using a dual column configuration where the second channel uses a INNOWax column yielding a different elution order compared to the 624 phase. Using the MSD in SIM overcomes this problem when using just the 624 phase.

For new drug development and scale-up of new formulations, the 5977 Series GC/MSD System can be a powerful tool. This system is also well suited for the development of generic methods that do not need to follow USP <467> guidelines. When unknown peaks or solvents are present, this system may be the best solution to use. Sensitivity in SIM is also a major advantage when looking for low-level impurities either known or unknown.

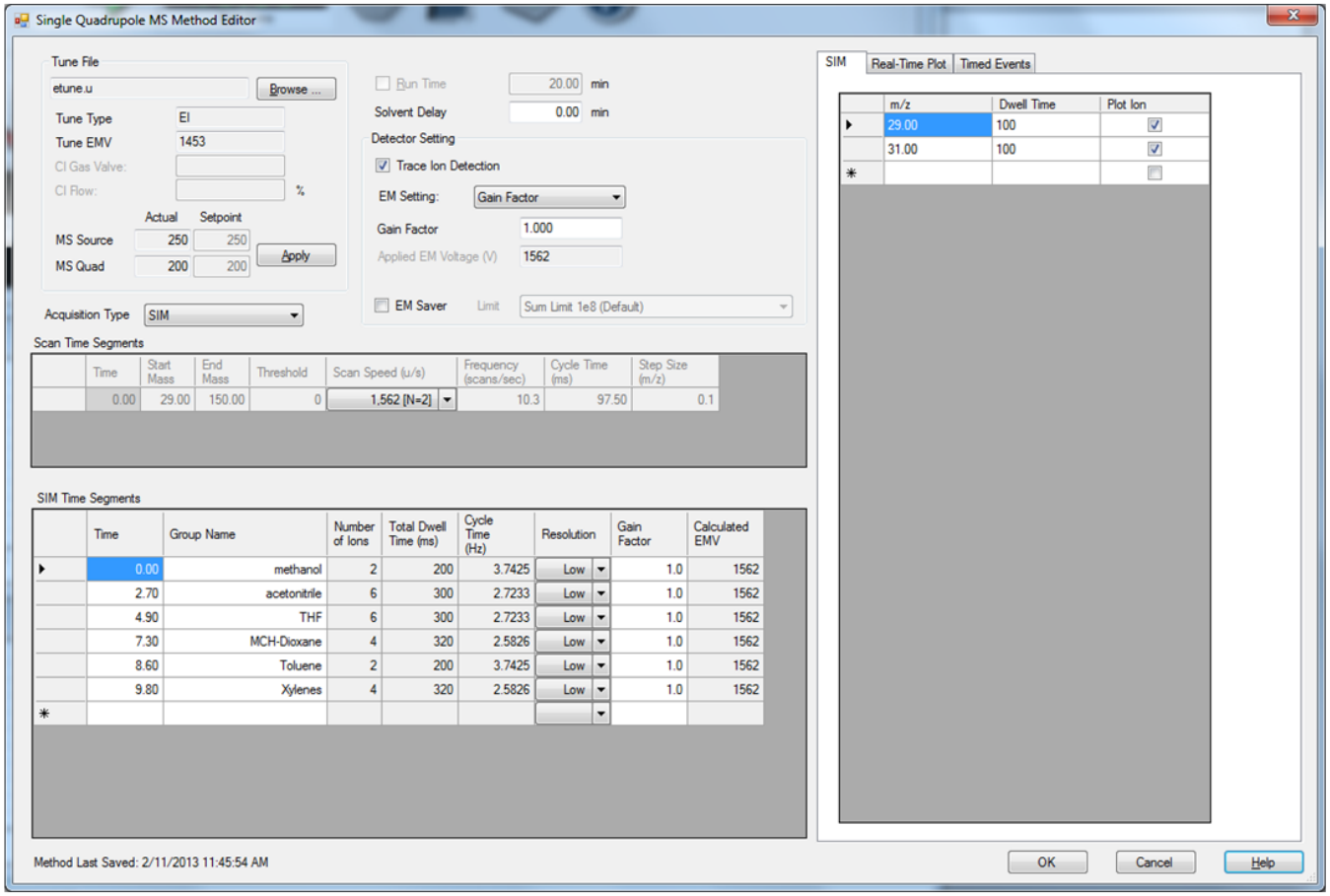

Figure 6. The SCAN/SIM setup pane (Class 2A) from MSD ChemStation acquisition.

Table 4. SIM groups for Class 2B solvents.

Group	Compound	SIM ions
1	Hexane	56,57
2	Nitromethane	46,61
3	Chloroform	83,85
4	Dimethoxyethane	45,60
5	Trichloroethene	130,132
6	Pyridine, 2-Hexanone	52,58,79,85
7	Tetralin	104,132

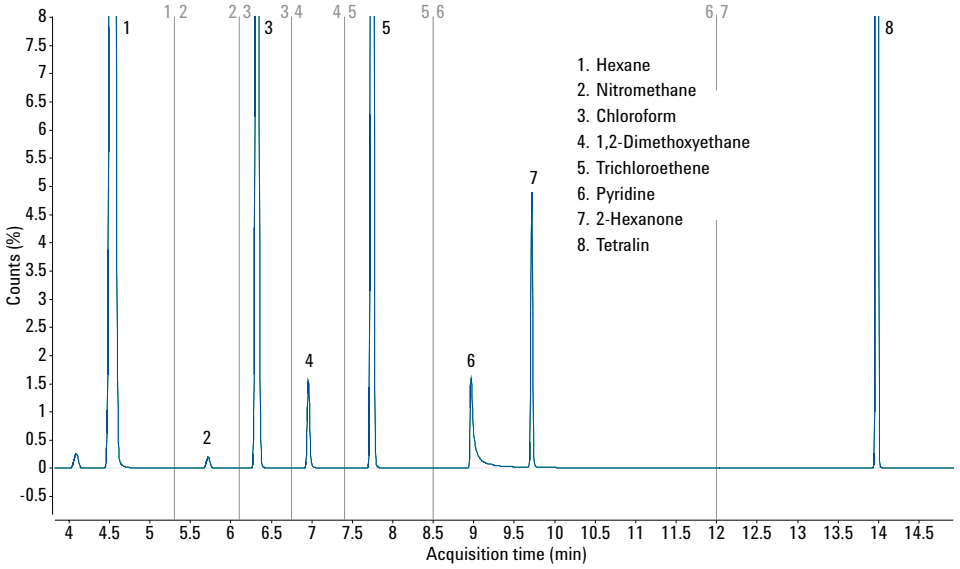

Figure 7. A typical SIM run for Class 2B solvents.

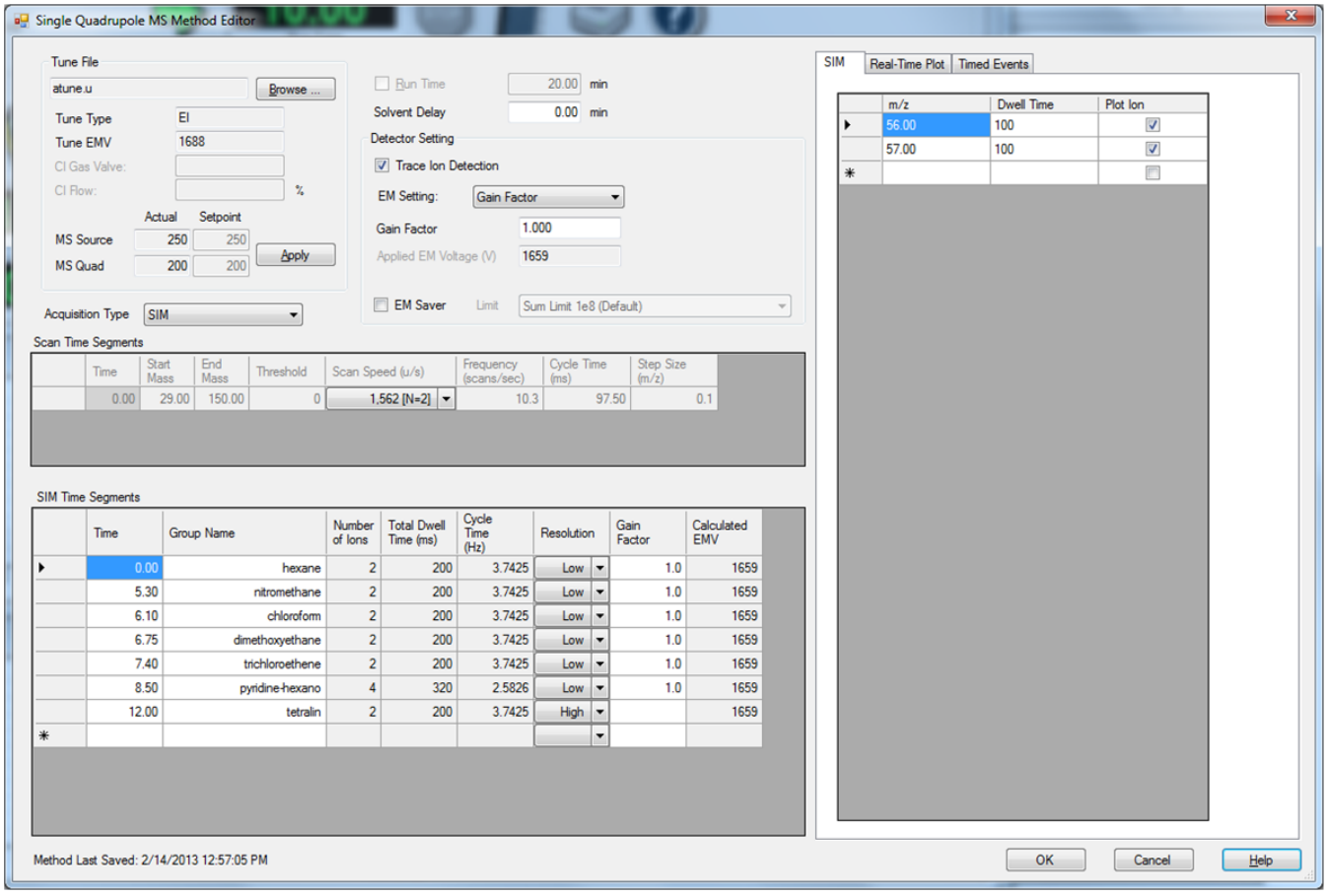

Figure 8. SCAN/SIM setup pane from the MSD ChemStation for Class 2B solvents.

Conclusion

The Agilent 5977 Series GC/MSD System/Agilent 7890B GC/Agilent 7697A headspace sampler is capable of outstanding repeatability for the analysis of residual solvents. Use of the MSD is a powerful analytical tool for investigation of solvent impurities in pharmaceutical starting materials including the API and excipients. It is especially useful in drug discovery and process scale-up where unknowns must be identified.

In the 7697A headspace sampler, an inert sample path, thermal zones with stability of better than ±0.1 °C of setpoint, and flexible EPC-controlled vial sampling all contribute to the system's performance. Carryover was nonexistent in this system. User programmable (flow rate and times) needle/loop purge, and vent line purge are used to effectively clean the system between runs.

The methods outlined in this work illustrate several possible strategies for the analysis of residual solvents using the 5977 Series GC/MSD system. Laboratories should perform system suitability studies and validate their proposed methods according to USP or ICH guidelines. The MSD configuration is particularity useful when the need for unknown identification arises, or in QA labs for unambiguous confirmation.

References

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