Application Note

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Analysis of USP <467> Residual Solvents of Class 1, Class 2, and Class 3 using the Agilent 8890 GC/ FID /5977B MSD System

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Abstract

An Agilent 8890 Gas Chromatograph (GC) configured with a flame ionization detector (FID) and a mass spectrometric detector (MSD) was used for the analysis of USP <467> residual solvents of Class 1, Class 2, and Class 3. There were 52 compounds with low boiling points introduced by an Agilent 7697A headspace sampler onto a DB-624 column, while 10 compounds with relatively high boiling points were introduced by the automatic liquid sampler onto a DB-WAX column. A purged two-way capillary flow technology (CFT) device was used to split the sample 1:1 onto FID and MSD.

This Application Note demonstrates excellent peak shape, resolution and great repeatability, which shows this FID and MSD dual-channel system is a powerful tool for qualitative and quantitative analysis of residual solvents.

Introduction

Analysis of residual solvents is a critical application in the pharmaceutical industry. Residual solvents have been classified into three main classes based on risk assessment by United States Pharmacopeia (USP) Method <467>.[1]

- Class 1 solvents, containing five compounds, should be avoided in manufacturing processes.
- Class 2 solvents contain 30 compounds, and should be limited.
- Class 3 solvents, containing 27 compounds, are considered lower risk.

In total, there are more than 60 compounds in the three classes. The compounds list of Pharmacopoeia of China (2015 edition)[2] is almost the same as USP <467> method.

Labs in the pharmaceutical industry normally use gas chromatography for residual solvents analysis. When unknown components appear in their routine job, MSD is a good choice for identification of volatile organic solvents. Usually GC and GC/MSD are two separate systems in the labs, and it may take a long time for users to transfer the method between the two systems that may use different carrier gas or columns. This Application Note used a single 8890 GC configured with both FID and MSD for the three classes of residual solvents analysis. Samples introduced by headspace or automatic liquid sampler were split 1:1 onto FID and MSD. FID or MSD can be used as the tools for quantitative analysis, while MSD also can be used for qualitative analysis of unknown components.

Experimental

This Application Note divided the compounds in the list of USP <467> method into two categories. One category was volatile compounds with a low boiling point, which were introduced into GC by headspace connecting to the back inlet; the other category was compounds with a relatively high boiling point, which were introduced into GC by automatic liquid sampler installed on the front inlet. An Agilent 8890 GC with an Agilent 5977B MSD equipped with FID, Agilent 7697A headspace, and Agilent 7693A automatic liquid sampler was used for the series of experiments. A purged two-way CFT device was used to split the column effluent 1:1 to the MSD and FID. Without changing the hardware, users can switch between headspace injection and liquid injection by replacing the columns. Figure 1 shows the schematics for the instrument setup. Tables 1 and 2 list the chromatographic conditions used for these analyses.

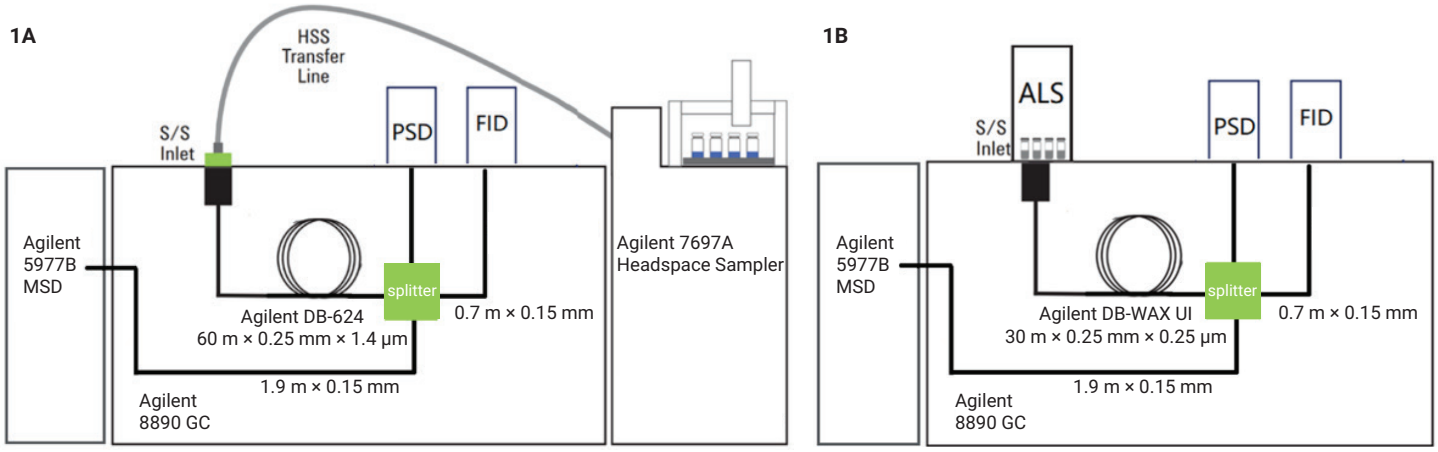

Figure 1. 1A is the system configuration for headspace injection connecting to the back inlet. 1B is the same system configuration for automatic liquid injection connecting to the front inlet.

Chromatographic conditions

Table 1. Headspace injection method.

Agilent 7697 A Headspace	
Parameter	Value
Vial Pressurization Gas	N_2
Loop Size	1 mL
Vial Size	20 mL
Vial Shaking	7
Vial Standby Flow	20 mL/min
Vial Equilibration Time	30 minutes
Inject Time	0.5 minute
Oven Temp	85 °C
Loop Temp	95 °C
Transfer Line	0.53 mm ID, deactivated fused silica (p/n 160-2535-5)
Transfer Line Temp	105 °C
Vial Fill Pressure	15 psi
Loop Fill Mode	Custom
Loop Ramp Rate	20 psi/min
Loop Final Pressure	4 psi
Loop Equilibration Time	0.1 minute
Agilent 8890 GC	
Parameter	Value
Inlet	SSL, 250 °C, split 10:1
Liner	Straight, deactivated, 2 mm ID (p/n 5181-8818)
CFT Device	Purged 2-way splitter (p/n G3180-60501), Split Ratio 1:1 MSD: FID
PSD	3.8 psi constant pressure
Column	Agilent DB-624 60 m × 0.25 mm, 1.4 µm (p/n 122-1364)
Carrier	Helium, 1 mL/min, constant flow
FID Restrictor	0.7 m × 0.15 mm id deactivated fused silica tubing (p/n 160-2625-10)
MSD Restrictor	1.9 m × 0.15 mm id deactivated fused silica tubing (p/n 160-2625-10)
Oven	40 °C (10 minutes), then 5 °C/min to 80 °C, then 12 °C/min to 220 °C (10 minutes)
FID	Temperature: 250 °C, Hydrogen: 30 mL/min, Air: 300 mL/min, Make-up gas (N_2): 25 mL/min
Transfer line temperature	250 °C
Agilent 5977B MSD	
Parameter	Value
Ionization Type	EI
Source Temperature	230 °C
Quad Temperature	150 °C
Drawout Plate	3 mm
Tune File	Atune.u
Acquisition Type	Scan
Solvent Delay	6 minutes
Relative Voltage	0

Table 2. Liquid injection method.

Agilent 8890 GC	
Parameter	Value
Inlet	SSL, 250 °C, split 30:1
Liner	Ultra Inert, split, low pressure drop, glass wool (p/n 5190-2295)
Injection Volume	0.5 µL, syringe (p/n 5181-8810)
CFT Device	Purged 2-way splitter (p/n G3180-60501), Split Ratio 1:1 MSD: FID
PSD	3.8 psi constant pressure
Column	Agilent DB-WAX UI 30 m × 0.25 mm, 0.25 µm (p/n 122-7032UI)
Carrier	Helium, 1 mL/min, constant flow
FID Restrictor	0.7 m × 0.15 mm id deactivated fused silica tubing
MSD Restrictor	1.9 m × 0.15 mm id deactivated fused silica tubing
Oven	40 °C, then 5 °C/min to 160 °C, then 10 °C/min to 220 °C (10 minutes)
FID	Temperature: 250 °C, Hydrogen: 30 mL/min, Air: 300 mL/min Make-up gas (N_2): 25 mL/min
Transfer Line Temperature	250 °C
Agilent 5977B MSD	
Parameter	Value
Ionization Type	EI
Source Temperature	230 °C
Quad Temperature	150 °C
Drawout Plate	3 mm
Tune File	Atune.u
Acquisition Type	Scan
Solvent Delay	6 minutes
Relative Voltage	0

Chemicals and standards

Three stock solutions of residual solvents in dimethyl sulfoxide (DMSO) were from Agilent Technologies:

- Class 1: p/n 5190-0490
- Class 2A: p/n 5190-0492
- Class 2C: p/n 5190-0493

The single standards of Class 2B and Class 3 compounds were purchased from ANPEL Scientific Instrument Co. Ltd. (Shanghai, China) and J&K Scientific Ltd.

Compounds in Table 3 were diluted in DMSO and water solution (v/v=50:50). The headspace vials were made at each calibration level by filling each vial with 5 mL of DMSO and water solution (v/v=50:50) and spiking varying amounts of stock solution to achieve the required levels. Compounds in Table 4 were diluted in water. Table A1 in Appendix A shows the concentrations of different levels for each compound.

Table 3. Results for 52 compounds following headspace analysis on an Agilent DB-624 column. (Continued on next page).

No.	Name	RT	*m/z*	Linearity Range (µg/mL)	R^2		Area RSD% L4 (n=8)	MDL (MSD) µg/mL
					MSD	FID		
1	Methanol	8.818	31	0.75 to 150	0.9998	0.9994	2.2	0.194
2	Pentane	11.251	43	0.5 to 100	0.9944	0.9997	2	0.143
3	Ethanol	11.73	31	2 to 100	0.9999	0.9998	1.2	0.514
4	Ethyl ether	12.142	74.1	0.5 to 100	0.9911	0.9998	4.3	0.147
5	1,1-Dichloroethene	13.083	61	0.004 to 0.8	0.9997	0.9986	1.7	0.003
6	Acetone	13.283	43	0.5 to 100	0.9999	0.9996	2.1	0.227
7	Isopropanol	13.854	45	1 to 200	0.9997	0.9979	4.3	0.245
8	Ethyl formate	13.873	45	1 to 200	0.9997	0.9979	4.3	0.245
9	Acetonitrile	14.39	41	0.1 to 20	0.9996	0.9984	4.2	0.032
10	Methyl acetate	14.564	43	0.5 to 100	0.9998	0.9998	2.7	0.424
11	Methylene chloride	14.947	84	0.15 to 30	0.9997	0.9997	2.1	0.033
12	*tert*-Butylmethyl ether	15.938	73	0.1 to 20	0.9988	0.9998	2.1	0.035
13	*trans*-1,2-Dichloroethene	15.979	95.9	0.236 to 47	0.9969	0.9998	1.7	0.065
14	Hexane	16.899	57	0.1 to 20	0.9995	0.9998	2.2	0.074
15	1-Propanol	17.712	31	0.5 to 100	0.9995	0.9996	2	0.180
16	Nitromethane	19	46	0.5 to 100	0.9999	0.9991	1.9	0.252
17	*cis*-1,2-Dichloroethene	19.21	96	0.236 to 47	0.9988	0.9999	2.5	0.045
18	2-Butanone	19.225	43	0.5 to 100	0.998	0.9999	2.3	0.147
19	Ethyl acetate	19.375	43	0.5 to 100	0.9986	0.9997	1.4	0.305
20	2-Butanol	19.688	45	0.5 to 100	0.9998	0.9999	2.4	0.237
21	Tetrahydrofuran	19.985	42	0.18 to 36	0.9998	0.9998	2.1	0.053
22	Chloroform	20.054	83	0.015 to 3	0.9997	0.9998	1.6	0.006
23	1,1,1-Trichloroethane	20.546	97	0.005 to 1	0.9999	0.9998	1.3	0.003
24	Cyclohexane	20.707	84	1.0 to 49 (195)*	0.9908	0.9997	1.8	0.188
25	Carbon tetrachloride	20.962	117	0.002 to 0.4	0.9998	0.9992	2.8	0.002
26	2-Methyl-1-propanol	21.119	43	0.5 to 100	0.9999	0.9999	2.1	0.494
27	1,2-Dimethoxyethane	21.265	45	0.5 to 100	0.9999	0.9995	1	0.256
28	Benzene	21.442	78	0.001 to 0.2	0.9995	0.9998	5.8	0.001
29	1,2-Dichloroethane	21.442	62	0.01 to 0.5	0.9989	0.9998	1.5	0.002
30	Isopropyl acetate	21.496	61	0.5 to 100	0.9985	0.9998	0.8	0.164
31	Heptane	21.956	71	0.1 to 20	0.9974	0.9996	2.4	0.034
32	1-Butanol	22.547	56	0.5 to 100	0.9994	0.9998	2.4	0.172
33	Trichloroethylene	22.791	130	0.015 to 3	0.9999	0.9999	1.8	0.007
34	Methylcyclohexane	23.208	83	0.3 to 15 (59)*	0.9989	0.9997	2.3	0.072
35	1,4-Dioxane	23.489	88	0.095 to 19	0.9999	0.9999	3.3	0.055
36	Propyl acetate	23.491	43	0.5 to 100	0.9966	0.9999	3	0.268
37	4-Methyl-2-pentanone	24.815	43	0.5 to 100	0.9985	0.9996	2.2	0.143
38	Isoamyl alcohol	24.879	55.1	0.5 to 100	0.9991	0.9996	2.4	0.256
39	Pyridine	25.024	79	2 to 100	0.9992	0.9997	2.1	0.502

Table 3. Results for 52 compounds following headspace analysis on an Agilent DB-624 column. (Continued).

No.	Name	RT	*m/z*	Linearity Range (µg/mL)	R^2		Area RSD% L4 (n=8)	MDL (MSD) µg/mL
					MSD	FID		
40	Toluene	25.196	91	0.22 to 22 (44)*	0.9964	0.9998	2.1	0.065
41	Isobutyl acetate	25.322	56	0.5 to 100	0.9958	0.9999	2.1	0.178
42	1-Pentanol	25.735	42	0.5 to 100	0.9996	0.9998	2.1	0.332
43	2-Hexanone	26.201	58	0.06 to 3	0.9995	0.9998	2.1	0.011
44	Butyl acetate	26.351	43	0.5 to 100	0.9957	0.9999	2.3	0.250
45	Tetrahydrothiophene	26.571	88	0.5 to 100	0.9996	0.9999	1.4	0.180
46	Chlorobenzene	27.503	112	0.09 to 18	0.9999	0.9997	2.5	0.022
47	Ethylbenzene	27.618	91	0.09 to 18	0.9986	0.9997	4.1	0.029
48	*m,p*-Xylene	27.782	106	0.4 to 40 (80)*	0.9963	0.9997	3.3	0.107
49	*o*-Xylene	28.393	91	0.05 to 10	0.9999	0.9996	2.6	0.017
50	Isopropylbenzene	28.904	105	0.1 to 20	0.9983	0.9996	2.4	0.039
51	Anisole	29.011	108	0.5 to 100	0.9999	0.9997	2.8	0.189
52	1,2,3,4-Tetrahydronaphthalene	33.814	104	0.015 to 3	0.9998	0.9993	2	0.005

* The values inside the brackets represent the linear maximum concentration for FID, and the minimum concentration of FID is the same as MSD.
The absence of an asterisk indicates the same linear range for MSD and FID.

Table 4. Results for 10 compounds following liquid injection on an Agilent DB-WAX column.

No.	Name	RT	*m/z*	Linearity Range (µg/mL)	R^2		Area RSD% L4 (n=8)	MDL (MSD) µg/mL
					MSD	FID		
53	2-Methoxyethanol	9.783	45	5 to 50	0.9984	0.9995	1.8	0.68
54	2-Ethoxyethanol	10.816	59	16 to 161	0.9973	0.9987	1.4	1.93
55	N,N-Dimethylformamide (DMF)	13.607	73	88.3 to 883	0.9997	0.9999	1	2.19
56	N,N-Dimethylacetamide (DMAC)	15.667	87	109.4 to 1094	0.9997	0.9996	1.3	2.58
57	Acetic acid	16.493	60	400 to 3000	0.9984	0.9997	1.7	90.12
58	Formic acid	17.774	46	400 to 3000	0.9995	0.9939	0.8	120
59	Ethylene glycol	20.652	31	62.2 to 622	0.9983	0.9982	1.8	4.44
60	N-Methylpyrrolidone	22.074	98	53 to 530	0.9995	0.9997	0.9	3.02
61	Formamide	24.157	45	22 to 221	0.9992	0.9986	2.3	2.11
62	Sulfolane	30.706	120	16 to 160	0.9994	0.9997	2.1	1.33

Results and discussion

1. Headspace injection analysis

The 52 compounds from the USP <467> list were introduced by headspace and resolved on an Agilent DB-624 analysis column in approximately 40 minutes. Splitting the column effluent to both an MSD and FID facilitated selectivity, identification, and confirmation of the 52 compounds from a single injection, thereby increasing laboratory productivity. Using GC/MS in full scan mode enabled identification of unknown residual solvents in drug products. The pharmaceutical industry usually uses FID for quantitative analysis. When an unknown compound appears, the retention time of the compound on MSD and FID is the same in this system. This unknown compound can be easily found in the chromatogram of MSD, then the qualitative work can be done by the library search function. Figure 2 shows good peak shapes for those compounds in both the GC/MS/SCAN and FID chromatograms.

Figure 2 shows that *tert*-butylmethyl ether and *trans*-1,2-dichloroethene; *cis*-1,2-dichloroethene and 2-butanone; tetrahydrofuran and chloroform; benzene, 1,2-dichloroethane and isopropyl acetate; 1,4-dioxane and propyl acetate; 4-methyl-2-pentanone and isoamyl alcohol are not well separated on the DB-624 column. The coeluting compounds do not share common MSD fragments, so while quantitation is challenging with an FID, the ions unique to each compound can be extracted and processed separately. Isopropanol and ethyl formate also coeluted on the DB-624 column, and they have the same quantitative ions. In this study, the two compounds were quantified together. If accurate quantification is required, other columns with different stationary phases can be chosen for separation.

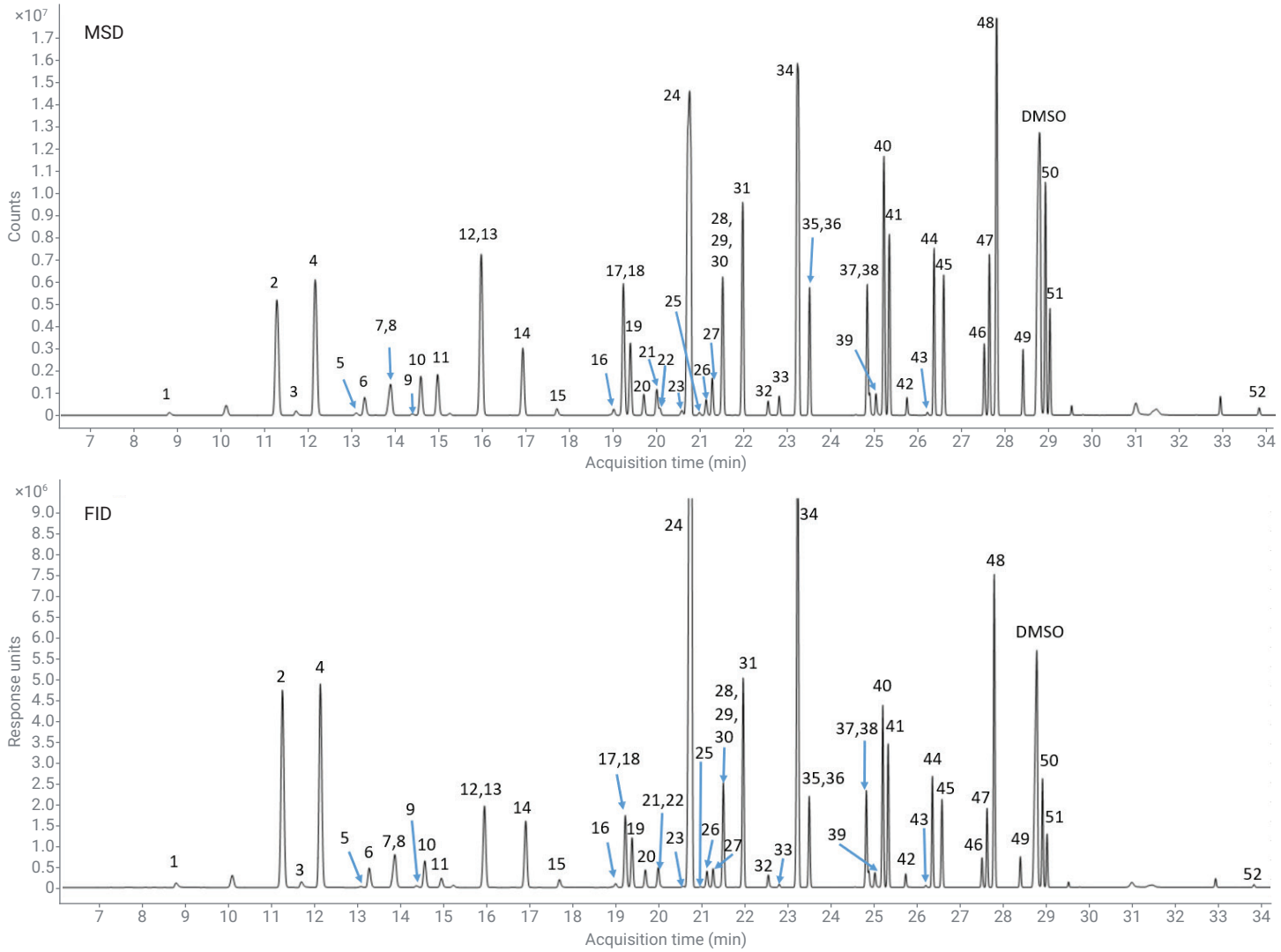

Figure 2. GC/MS-SCAN and FID Chromatogram of 52 compounds of standard solution (Level 7) on an Agilent DB-624 column.
The effluent split ration is MSD: FID= 1:1.

Selection of dilution solvent for the headspace injection

Methanol, acetone, N,N-dimethylformamide (DMF), and DMSO are commonly used as diluted solvents of volatile organic solvents. In this study, methanol, acetone, and DMF were not used because they are the target compounds. The solvent of Class 1 and Class 2 stock solutions is DMSO, and DMSO is mutually soluble with most of the residual solvents, thus DMSO was chosen as the base solvent. When headspace injection was used, higher sensitivity could be obtained for the less polar organic compounds dissolving in the more polar solvent, such as water. However, factors such as solubility should be noted. The volume ratio of DMSO to water 50:50 was adopted as the final dilution solvent.

Table 3 shows the results for the 52 compounds. Because of the concentration limit of the purchased standards mixtures, the linearity range of each compound is different, as shown in Table 3. Table A1 in Appendix A specifies the concentrations of each compound in the different levels analyzed. Linearity across the range studied gave R^2 values of greater than 0.99 for the 52 compounds on both MSD and FID, with most having R^2 values greater than 0.999. Repeatability was evaluated by eight consecutive injections at the concentration of a midlevel calibration standard (Level 4). Table 3 illustrates that for most compounds, the area %RSD by MSD was well below 5.8%. MDL values were calculated from the standard deviation of eight replicate runs of a low-level calibration standard (Level 2). The details are also shown in Table 3.

2. Liquid injection analysis

Most of the Class 2 and Class 3 residual solvents can be detected by the headspace injection conditions previously described. However, the headspace method is not suitable for all the residual solvents, especially for the compounds with a relatively high boiling point from Class 2 and water-soluble acids from Class 3. Those compounds were determined by liquid injection for higher sensitivity.

Figure 3 shows an example chromatogram of GC/MS-SCAN and FID acquired simultaneously. The DB-WAX column showed excellent resolution for all the compounds. The response of some compounds such as formic acid, which have low carbon number on MSD, was higher than on FID. For those compounds, MSD is a good choice for improving the sensitivity.

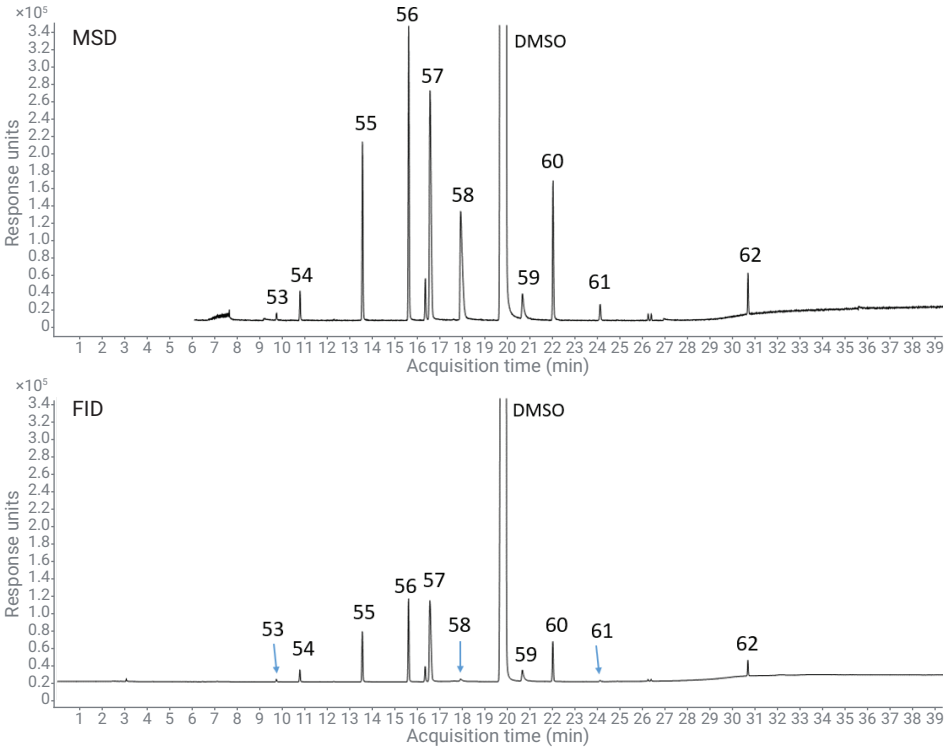

Figure 3. GC/MS-SCAN and FID Chromatogram of 10 compounds of standard solution (Level 5) on an Agilent DB-WAX column. The effluent split ration is MSD:FID = 1:1.

Influence of DMSO on retention time of acids for liquid injection

In this study, 10 compound mixtures were made from Class 2C standard, formic acid, and acetic acid single standards. The solvent of Class 2C was DMSO, and the two acids were pure solvent. To achieve the required levels, six vials were made at each calibration level by spiking varying amounts of Class 2C and acids in water. This means that the higher the concentration of the sample, the higher the amount of DMSO. As Figure 4 shows, the retention time (RT) of formic acid and acetic acid shifted back with the increase of the concentration of the sample, while the RT of Class 2C compounds such as N,N-Dimethylacetamide (DMAC) and ethylene glycol remained the same in different levels. If the same RT of acids in different levels is needed, it is necessary to keep the amount of DMSO the same in different levels, as shown in Figure 5.

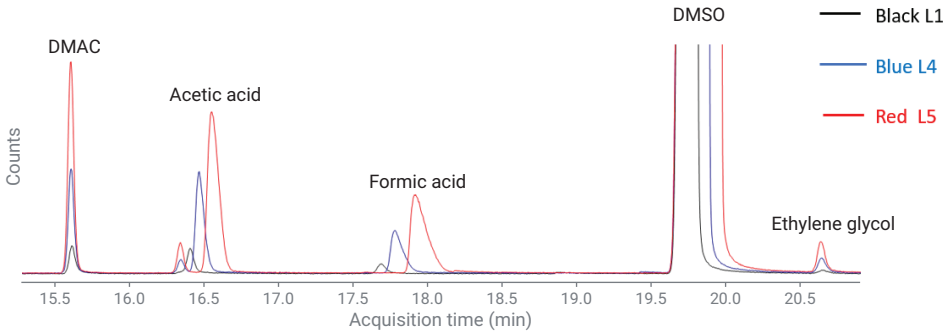

Figure 4. The overlaid chromatogram of calibration levels of Level 1, Level 4, and Level 5 with different amounts of DMSO in the solutions.

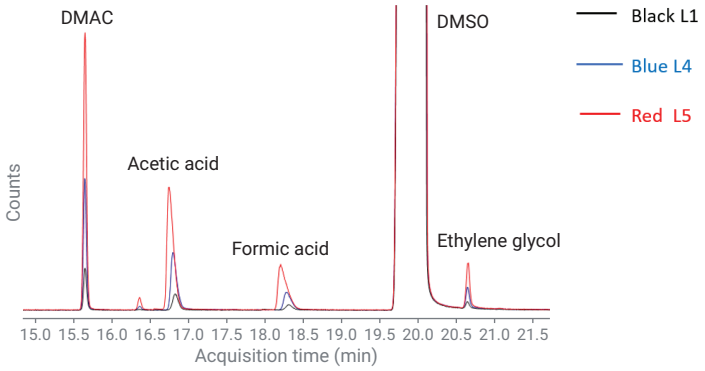

Figure 5. The overlaid chromatogram of calibration levels of Level 1, Level 4, and Level 5 with the same amount of DMSO in the solutions.

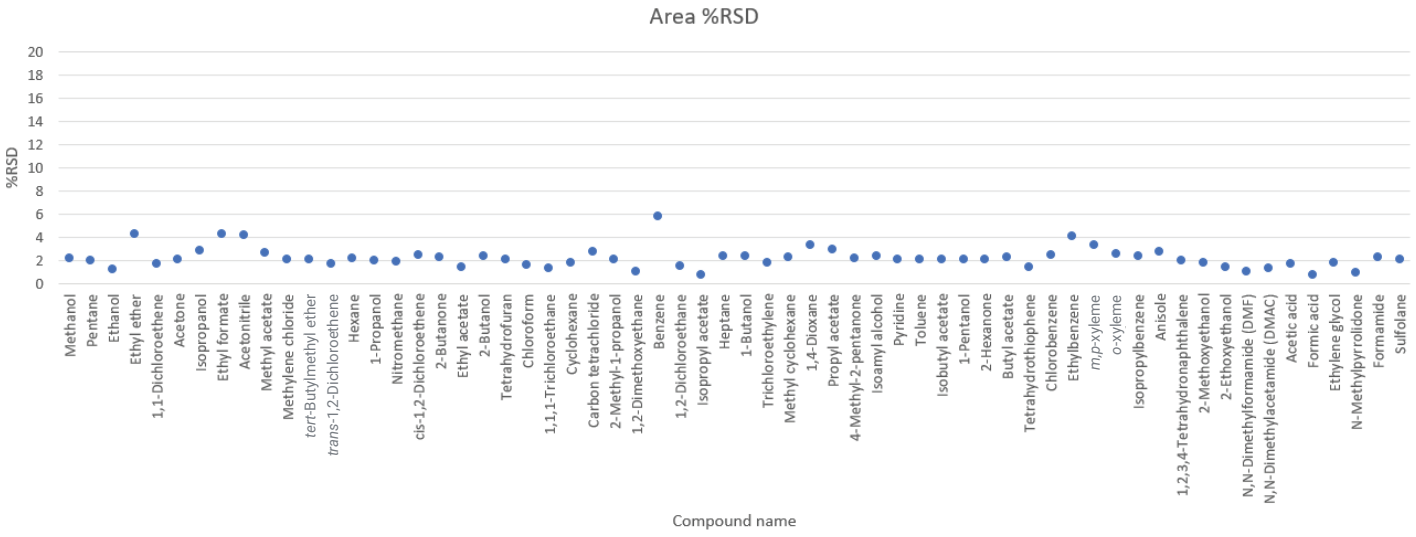

Figure 6. Area %RSD results for all the compounds.

Table 4 shows the correlation coefficients for the 10 compounds. R^2 values were better than 0.9939 on both MSD and FID. Repeatability was tested using eight injections of the standard mixture at the concentration of Level 4. For all compounds, the area %RSD was well below 2.3%. MDL values were calculated from the standard deviation of eight replicate runs of the Level 1 calibration standard. These details are also shown in Table 4.

Conclusion

Residual solvents of Class 1, 2, and 3 were tested using the Agilent 8890 GC/FID/MSD system. For new drug development and quality control, FID and MSD dual-channel configurations can be powerful tools for solvent residue analysis. MSD analysis can avoid the uncertainty of more than 60 solvents involved in drug production. When unknown peaks or unknown solvents appear, this system is the best solution for solvent identification and quantification.

References

1. USP 32-NF 27, General Chapter USP <467> Organic volatile impurities, United States Pharmacopeia. Pharmacopoeia Convention Inc., Rockville, MD, 8/2009.
2. Chinese Pharmacopeia (2015). Appendix ⅧSolvent residue determination, China.

Appendix A

Table A1. The concentration of each compound in the different levels analyzed. (Continued on next page).

No.	Name	Concentration (µg/mL)						
		L1	L2	L3	L4	L5	L6	L7
1	Methanol	0.75	3	7.5	14	37.5	75	150
2	Pentane	0.5	2	5	10	25	50	100
3	Ethanol	NA	2	5	10	25	50	100
4	Ethyl ether	0.5	2	5	10	25	50	100
5	1,1-Dichloroethene	0.004	0.016	0.04	0.08	0.2	0.4	0.8
6	Acetone	0.5	2	5	10	25	50	100
7	Isopropanol	0.5	2	5	10	25	50	100
8	Ethyl formate	0.5	2	5	10	25	50	100
9	Acetonitrile	0.10	0.4	1	2	5	10	20
10	Methyl acetate	0.5	2	5	10	25	50	100
11	Methylene chloride	0.15	0.6	1.5	3	7.5	15	30
12	tert-Butylmethyl ether	0.1	0.4	1	2	5	10	20
13	*trans*-1,2-Dichloroethene	0.236	0.944	2.36	4.72	11.8	23.5	47
14	Hexane	0.1	0.4	1	2	5	10	20
15	1-Propanol	0.5	2	5	10	25	50	100
16	Nitromethane	0.5	2	5	10	25	50	100
17	*cis*-1,2-Dichloroethene	0.236	0.944	2.36	4.72	11.8	23.5	47
18	2-Butanone	0.5	2	5	10	25	50	100
19	Ethyl acetate	0.5	2	5	10	25	50	100
20	2-Butanol	0.5	2	5	10	25	50	100
21	Tetrahydrofuran	0.18	0.72	1.8	3.6	9	18	36
22	Chloroform	0.015	0.06	0.15	0.3	0.75	1.5	3
23	1,1,1-Trichloroethane	0.005	0.02	0.05	0.1	0.25	0.5	1
24	Cyclohexane	1	4	10	20	49	97.5	195
25	Carbon tetrachloride	0.002	0.008	0.02	0.04	0.1	0.2	0.4
26	2-Methyl-1-propanol	0.5	2	5	10	25	50	100
27	1,2-Dimethoxyethane	0.5	2	5	10	25	50	100
28	Benzene	0.001	0.004	0.01	0.02	0.05	0.1	0.2
29	1,2-Dichloroethane	NA	0.01	0.025	0.05	0.125	0.25	0.5
30	Isopropyl acetate	0.5	2	5	10	25	50	100
31	Heptane	0.1	0.4	1	2	5	10	20
32	1-Butanol	0.5	2	5	10	25	50	100
33	Trichloroethylene	0.015	0.06	0.15	0.3	0.75	1.5	3
34	Methylcyclohexane	0.3	1.2	3	6	15	29.5	59
35	1,4-Dioxane	0.095	0.38	0.95	1.9	4.75	9.5	19
36	Propyl acetate	0.5	2	5	10	25	50	100
37	4-Methyl-2-pentanone	0.5	2	5	10	25	50	100
38	Isoamyl alcohol	0.5	2	5	10	25	50	100
39	Pyridine	NA	2	5	10	25	50	100

Table A1. The concentration of each compound in the different levels analyzed. (Continued).

No.	Name	Concentration (µg/mL)						
		L1	L2	L3	L4	L5	L6	L7
40	Toluene	0.22	0.88	2.2	4.4	11	22	44
41	Isobutyl acetate	0.5	2	5	10	25	50	100
42	1-Pentanol	0.5	2	5	10	25	50	100
43	2-Hexanone	NA	0.06	0.15	0.3	0.75	1.5	3
44	Butyl acetate	0.5	2	5	10	25	50	100
45	Tetrahydrothiophene	0.5	2	5	10	25	50	100
46	Chlorobenzene	0.09	0.36	0.9	1.8	4.5	9	18
47	Ethylbenzene	0.09	0.36	0.9	1.8	4.6	9	18
48	m,p-Xylene	0.4	1.6	4	8	20	40	80
49	o-Xylene	0.05	0.2	0.5	1	2.5	5	10
50	Isopropylbenzene	0.1	0.4	1	2	5	10	20
51	Anisole	0.5	2	5	10	25	50	100
52	1,2,3,4-Tetrahydronaphthalene	0.015	0.06	0.15	0.3	0.75	1.5	3
53	2-Methoxyethanol	5	6.3	8.3	12.5	25	50	NA
54	2-Ethoxyethanol	16	20.1	26.8	40.3	80	161	NA
55	N,N-Dimethylformamide	88.3	110.4	147.2	220.8	441	883	NA
56	N,N-Dimethylacetamide	109.4	136.8	182.3	273.5	547	1094	NA
57	Acetic acid	400	600	800	1000	2000	3000	NA
58	Formic acid	400	600	800	1000	2000	3000	NA
59	Ethylene glycol	62.2	77.8	103.7	155.5	311	622	NA
60	N-Methylpyrrolidone	53	66.3	88.3	132.5	265	530	NA
61	Formamide	22	27.6	36.8	55.3	110	221	NA
62	Sulfolane	16	20	26.7	40	80	160	NA

NA: The inclusion of NA indicates that this concentration level was not involved in the calculation of linearity.

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