Application Note

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Analysis of Organic Volatile Impurities in Drug Products and Drug Substances

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Abstract

This application note highlights a solution for the determination of several organic volatile impurities in drug products and drug substances. An Agilent 7697A headspace sampler coupled to an Agilent 7890B GC system is used. The method uses an Agilent J&W DB-624 GC column with 30 m length, 0.32 mm id, and 1.8 µm film thickness. The method analyzes several residual solvents in 30 minutes with sufficient separation for all the solvents tested. The method offers excellent sensitivity and linearity from the limit of quantitation (LOQ, 10% of ICH limit) to 200%. The method was validated per ICH Q3C (R6) guidelines.[1] Relative standard deviation (RSD) of six consecutive injections at LOQ level ranged from 1.39 to 12.08%. Specificity tests indicated the absence of interferences. A single method can determine the concentration of solvents that belong to Class 2 and Class 3 simultaneously when both classes of solvents are present in a sample. This method was developed and validated as an alternative method to USP 467, with the benefit of faster analysis.

Introduction

Organic solvents constitute a major fraction in the synthesis of pharmaceutical products and cannot always be eliminated during the manufacturing processes. All drug substances, intermediates, excipients, and the final product must be monitored. Therefore, all products must be tested to assess whether the solvents used during the manufacturing processes are within the accepted limits. Quality assurance laboratories routinely use the United States Pharmacopeia (USP) Method <467>.[2] The method uses gas chromatography with headspace-based sample introduction.

The USP <467> monograph specifies the different classes of solvents per their toxicity, sets the concentration limits according to their health hazard, and describes the assay procedure for the solvents. A complete list of all the solvents that may be used in manufacturing processes is not mentioned under these classes. Therefore, the final products should be screened according to the solvents used during their specific manufacturing process.

Analytical methods that deviate from the USP monograph can also be used for the evaluation of pharmaceutical products. However, these methods should be thoroughly validated and their equivalence to the USP method should also be established. In this study, a single method was used to separate 29 solvents, including Class 2 and Class 3 solvents, and the method was validated per ICH Q3C (R6) guidelines. The residual solvents chosen for method development are common process solvents and impurities. The following considerations were kept in mind while defining the method scope:

- Minimizing the instrument presetup risk, so that laboratory incidents can be reduced
- Using a single column setup instead of multiple columns to enhance laboratory productivity
- Using a wider method scope to help with easy identification of cross-contamination by other solvents
- Increasing throughput with a shorter 30-minute analysis that uses a single standard mixture of compounds, as opposed to the 60-minute USP method for individual solvent classes

Experimental

Sample preparation

The active pharmaceutical ingredients (APIs) and drug products tested for this analysis included ticagrelor, telmisartan, vildagliptin, brivaracetam, favipiravir, polmacoxib, bictegravir, tofacitinib citrate, linagliptin, and posaconazole. The analysis can also be used for other products where the same process solvents have been used. A portion of 100 mg of the sample was weighed accurately into a 20 mL headspace vial, 1 mL of N-methyl-2-pyrrolidinone (NMP) was added via volumetric pipette, and the sample was shaken gently.

Standard preparation

The standard stock was diluted appropriately to obtain a calibration solution of the following concentrations, which are listed in Table 1.

Instrumentation

Analysis was performed using a 7890B GC system. The GC was configured with a 7697A headspace sampler connected to a split/splitless inlet (SSL). From the inlet, a J&W DB-624 GC column with dimensions 30 m × 0.32 mm id, 1.8 µm was connected to the detector. Data acquisition was carried out using Shimadzu LabSolutions.

Tables 2 and 3 display the GC and headspace parameters.

Table 1. Preparation of standard solutions.

	Solvent	Concentration (µg/mL)
1	Acetaldehyde	100
2	*t*-Butanol	100
3	Propyl acetate	100
4	Methyl isobutyl ketone	100
5	N-Methylmorpholine	100
6	Mesityl oxide	100
7	N,N-Dimethylacetamide	109
8	Acetonitrile	41
9	Dichloromethane	60
10	*n*-Hexane	29
11	Diisopropyl ether	10
12	Tetrahydrofuran	72
13	Methanol	300
14	Cyclohexane	388
15	1,4-Dioxane	38

	Solvent	Concentration (µg/mL)
16	Toluene	89
17	Dimethylformamide	88
18	*o*-Xylene	19.52
19	Ethanol	500
20	Ethyl ether	500
21	Acetone	500
22	Isopropyl alcohol	500
23	Methyl *t*-butyl ether	500
24	Methyl ethyl ketone	500
25	Ethyl acetate	500
26	Isopropyl acetate	500
27	*n*-Heptane	500
28	1-Butanol	500
29	Dimethyl sulfoxide	500

Results and discussion

The compounds were separated sufficiently, and the target peaks were well resolved. A blank and a standard chromatogram are shown in Figure 1. There are no interferences in the blank chromatogram at the solvent retention times. Figure 2 shows the standard separation at LOQ. The retention times and relative retention times for all solvents are listed in Table 4.

Table 2. GC parameters.

Parameter	Value
GC System	Agilent 7890B GC with Agilent 7697A headspace sampler
Column	Agilent J&W DB-624, 30 m × 0.32 mm id, 1.8 µm (p/n 123-1334)
Carrier Gas	Nitrogen
Column Flow	1.4 mL/min
Injection Volume	1,000 µL
Split Ratio	1:10
Run Time	30 min
Hydrogen	40 mL/min
Air	400 mL/min
Makeup Flow	40 mL/min
Sample Concentration	100 mg/mL
Injector Temperature	180 °C
Detector Temperature	250 °C
Oven Program	40 °C, hold 5 min 4 °C/min to 60 °C, hold 5 min 5 °C/min to 85 °C 25 °C/min to 220 °C, hold 4.6 min

Table 3. Headspace sampler parameters.

Parameter	Value
Vial Temperature	90 °C
Loop Temperature	100 °C
Transfer Line Temperature	110 °C
Vial Equilibration Time	30 min
GC Cycle Time	40 min
Pressurize Time	0.2 min
Loop Equilibration Time	0.05 min
Loop Fill Time	0.2 min
Inject Time	1 min
Vial Shake	Medium
Headspace Vial Capacity	20 mL
Diluent	N-Methyl-2-pyrrolidinone (NMP)

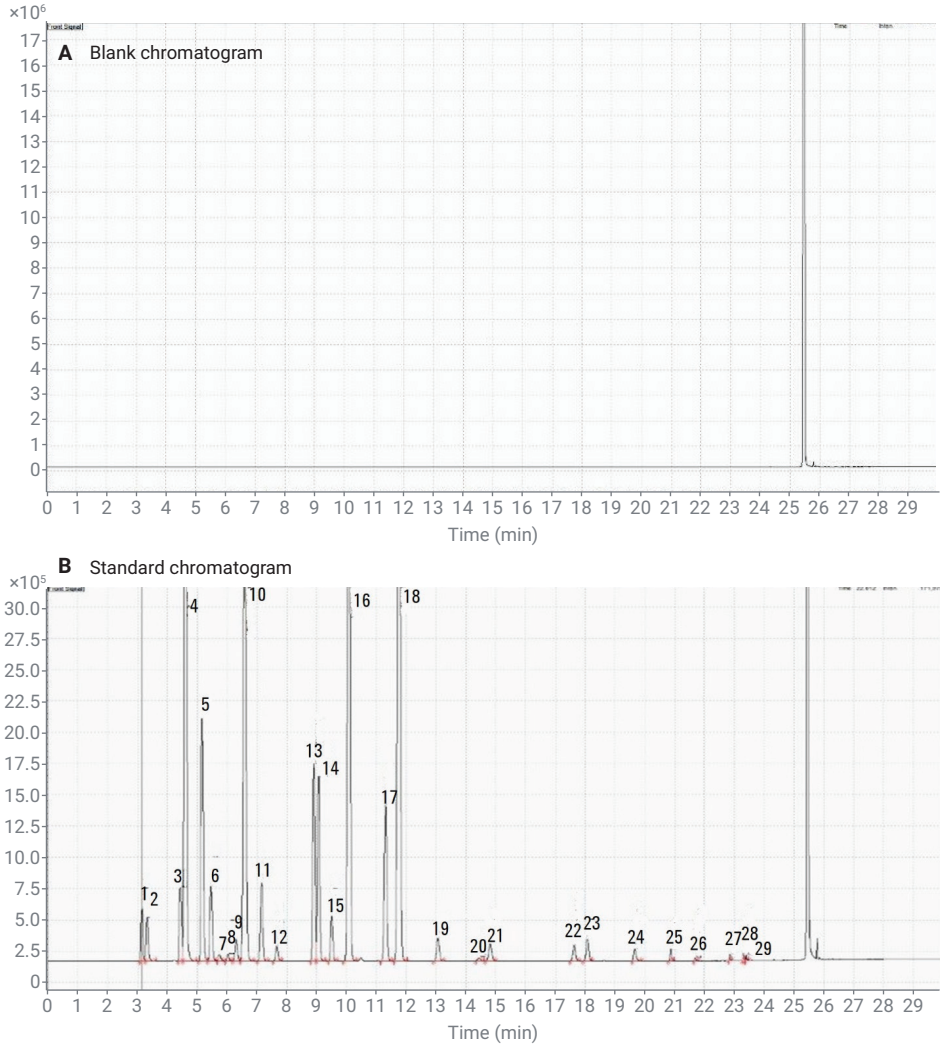

Figure 1. Blank and standard chromatograms on an Agilent 7890 GC system.

As per the ICH Q3C (R6) guidelines, the following acceptance criteria were considered during method development:

- Percent relative standard deviation (% RSD) calculated for peak areas of the initial six injections of standard solution should be less than 15.0.
- Resolution between any two adjacent peaks in the standard solution is greater than 1.0.
- Cumulative % RSD of peak areas of the initial six standard injections and online standard injection should be less than 15.0.
- There is no interference in the blank sample at the retention times of the standard solvents.
- Correlation coefficient of each solvent is greater than 0.98.
- There is no systematic trend in residuals, i.e. not more than five points on one side of the line continuously.
- The residuals of each solvent with respect to the calibration curve are within ±15% from the expected value at 100% test concentration.
- The % RSD calculated for the area of each solvent from each level of three replicate injections is less than 15.
- The % RSD calculated for the area of each solvent for low level (LOQ) and high level (200%) standards is less than 15.

Calibration curves were generated using a linear fit. The validation guidelines require the correlation coefficient (R^2) to be greater than 0.98. Excellent linearities with R^2 >0.996 were obtained in this study for all impurities, as shown in Figure 3 for a few example impurities.

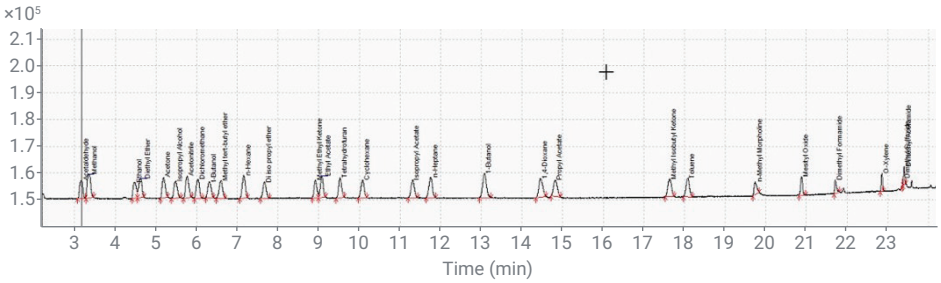

Figure 2. Chromatogram of 29 solvents at LOQ on an Agilent 7890 GC system.

Table 4. Solvent retention times (RT) and their relative retention times (RRT) with respect to methanol.

Peak ID	Solvent	RT (min)	RRT	ICH Limit (ppm)
1	*Acetaldehyde	3.15	0.95	1,000
2	Methanol	3.32	1.00	3,000
3	Ethanol	4.43	1.33	5,000
4	Diethyl ether	4.60	1.39	5,000
5	Acetone	5.16	1.55	5,000
6	Isopropyl alcohol	5.46	1.64	5,000
7	Acetonitrile	5.74	1.73	410
8	Dichloromethane	6.02	1.81	600
9	*t-Butanol	6.30	1.90	1,000
10	Methyl *t*-butyl ether	6.59	1.98	5,000
11	*n*-Hexane	7.15	2.15	290
12	*Diisopropyl ether	7.66	2.31	100
13	Methyl ethyl ketone	8.90	2.68	5,000
14	Ethyl acetate	9.06	2.73	5,000
15	Tetrahydrofuran	9.50	2.86	720
16	Cyclohexane	10.08	3.04	3,880
17	Isopropyl acetate	11.31	3.41	5,000
18	*n*-Heptane	11.76	3.54	5,000
19	1-Butanol	13.06	3.93	5,000
20	1,4-Dioxane	14.44	4.35	380
21	*Propyl acetate	14.81	4.46	1,000
22	*Methyl isobutyl ketone	17.63	5.31	1,000
23	Toluene	18.08	5.45	890
24	*N-Methylmorpholine	19.66	5.92	1,000
25	*Mesityl oxide	20.87	6.29	1,000
26	Dimethylformamide	21.68	6.53	880
27	*o-Xylene	22.85	6.88	195
28	Dimethyl sulfoxide	23.30	7.02	5,000
29	N,N-Dimethylacetamide	23.39	7.05	1,090

* In the absence of ICH guidelines, the limits have been calculated on the basis of daily dose.

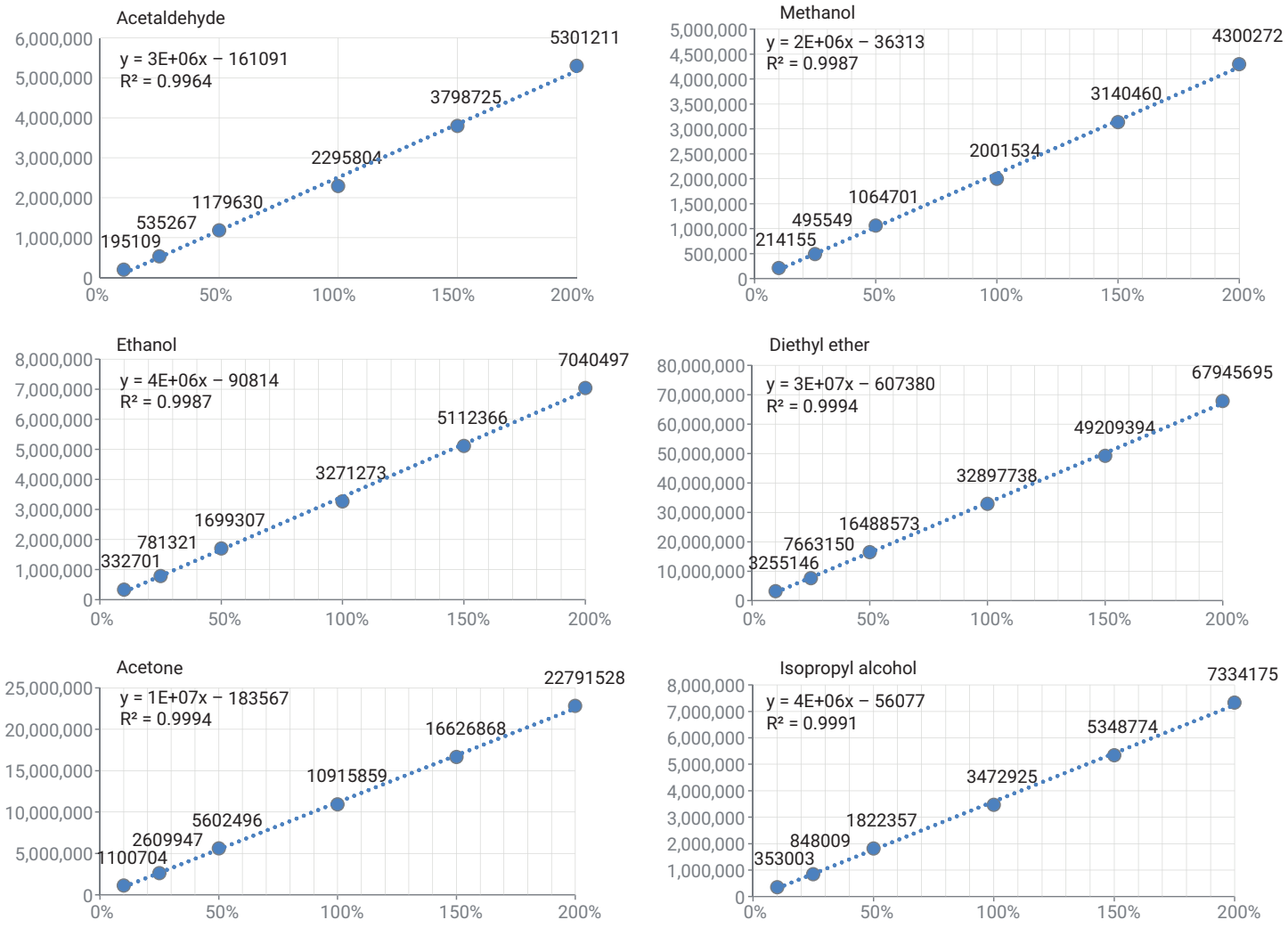

Figure 3. Calibration curves of impurities using an Agilent 7890B GC system.

The RSD for six replicate injections of the LOQ mixture was evaluated and found to be less than 7%. The individual RSDs and peak resolution are summarized in Table 5.

The resolution between the peaks is shown in Figure 4 in two sections (A) from RT 2.5 to 14 minutes and (B)12.75 to 24 minutes.

Robustness of the analytical method was tested by deliberate variation of method parameters, as follows:

Effect of variation in carrier gas flow rate:

a) Change the column flow to 1.26 mL/min instead of 1.4 mL/min.

b) Change the column flow to 1.54 mL/min instead of 1.4 mL/min.

Effect of variation in headspace incubation temperature ±2 °C:

a) Decrease the headspace incubation temperature by 2 °C.

b) Increase the headspace incubation temperature by 2 °C.

Robustness studies indicated <15% cumulative RSDs due to change of column flow and change in headspace incubation temperature.

Table 5. Peak resolution and % RSD for six injections of LOQ level standard.

Solvent	Peak Area (Inj. 1)	Peak Area (Inj. 2)	Peak Area (Inj. 3)	Peak Area (Inj. 4)	Peak Area (Inj. 5)	Peak Area (Inj. 6)	% RSD	Resolution (USP)
Acetaldehyde	191,522	191,902	202,779	195,138	190,948	198,362	2.40	NA
Methanol	207,575	213,758	219,505	206,939	224,261	212,891	3.15	1.38
Ethanol	322,549	333,070	342,485	329,037	362,464	332,792	4.16	8.74
Diethyl Ether	3,225,298	3,234,603	3,305,537	3,226,521	3,321,148	3,219,703	1.39	1.31
Acetone	1,079,044	1,096,235	1,126,832	1,086,973	1,142,441	1,099,627	2.21	4.08
Isopropyl Alcohol	344,714	352,558	361,737	351,793	380,909	354,952	3.52	4.11
Acetonitrile	28,555	28,494	30,067	28,304	31,849	28,678	4.74	2.09
Dichloromethane	29,050	29,898	29,801	28,972	31,437	29,525	3.01	2.12
t-Butanol	104,348	106,755	109,924	106,906	115,267	107,501	3.49	1.87
Methyl *t*-Butyl Ether	2,811,481	2,844,833	2,905,535	2,831,132	2,950,117	2,840,395	1.84	1.93
n-Hexane	323,990	325,656	331,805	325,630	337,162	324,363	1.61	3.93
Diisopropyl Ether	60,022	61,270	61,795	59,886	62,363	60,570	1.63	3.46
Methyl Ethyl Ketone	779,084	796,475	818,922	793,189	844,762	799,239	2.88	8.91
Ethyl Acetate	731,987	748,006	766,919	743,276	786,018	749,034	2.55	1.27
Tetrahydrofuran	178,534	182,388	185,553	182,473	181,605	184,160	1.31	3.41
Cyclohexane	3,141,275	3,181,159	3,252,866	3,164,366	3,303,971	3,182,604	1.92	4.26
Isopropyl Acetate	733,491	750,468	770,106	745,992	792,985	753,583	2.76	8.10
n-Heptane	3,984,861	4,039,954	4,130,452	4,019,136	4,194,878	4,075,326	1.90	2.97
1-Butanol	126,301	129,168	135,852	136,692	154,536	130,699	7.46	7.87
1,4-Dioxane	15,870	16,127	19,075	16,469	18,113	18,227	7.65	7.88
Propyl Acetate	100,471	103,010	107,719	103,040	111,801	104,496	3.86	2.00
Methyl Isobutyl Ketone	86,323	87,318	89,294	86,997	94,171	86,137	3.46	15.67
Toluene	126,603	131,294	134,073	131,089	142,038	130,890	3.90	2.86
N-Methylmorpholine	44,680	44,007	46,065	46,745	51,754	47,749	5.91	10.02
Mesityl Oxide	34,905	36,486	36,755	36,540	41,578	36,365	6.17	10.42
Dimethylformamide	4,610	4,459	4,870	4,955	5,170	5,175	5.99	10.07
o-Xylene	11,910	1,2059	12,655	12,532	13,944	12,114	5.96	19.52
Dimethyl Sulfoxide	9,852	10,902	11,542	12,282	11,823	11,055	7.54	8.12
N,N-Dimethylacetamide	6,918	6,085	6,054	5,517	5,828	6,097	7.65	2.15

The method involving 29 solvents was initially validated without sample matrix, then followed by validation with each drug substance. Real samples were analyzed using the validated method previously described, and the results were found to be in congruence with the methods laid out in USP <467>.

Conclusion

The analytical method described in this application note is used for the determination of general residual solvents. The method meets the acceptance criteria for analytical parameters such as specificity, quantitation limit, detection limit, linearity and range, solution stability, robustness, and intermediate precision. Therefore, this method can be used for routine analysis of volatile organic impurities in drug substances, intermediates, and drug products. The method is considerably shorter than the method laid out in USP monograph <467> and can therefore be used to increase laboratory productivity.

References

1. Impurities: Guideline for Residual Solvents Q3C(R6). International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use **2016**.
2. USP 32-NF 27, General Chapter USP <467> Residual Solvents/Organic Volatile Impurities. United States Pharmacopeia.

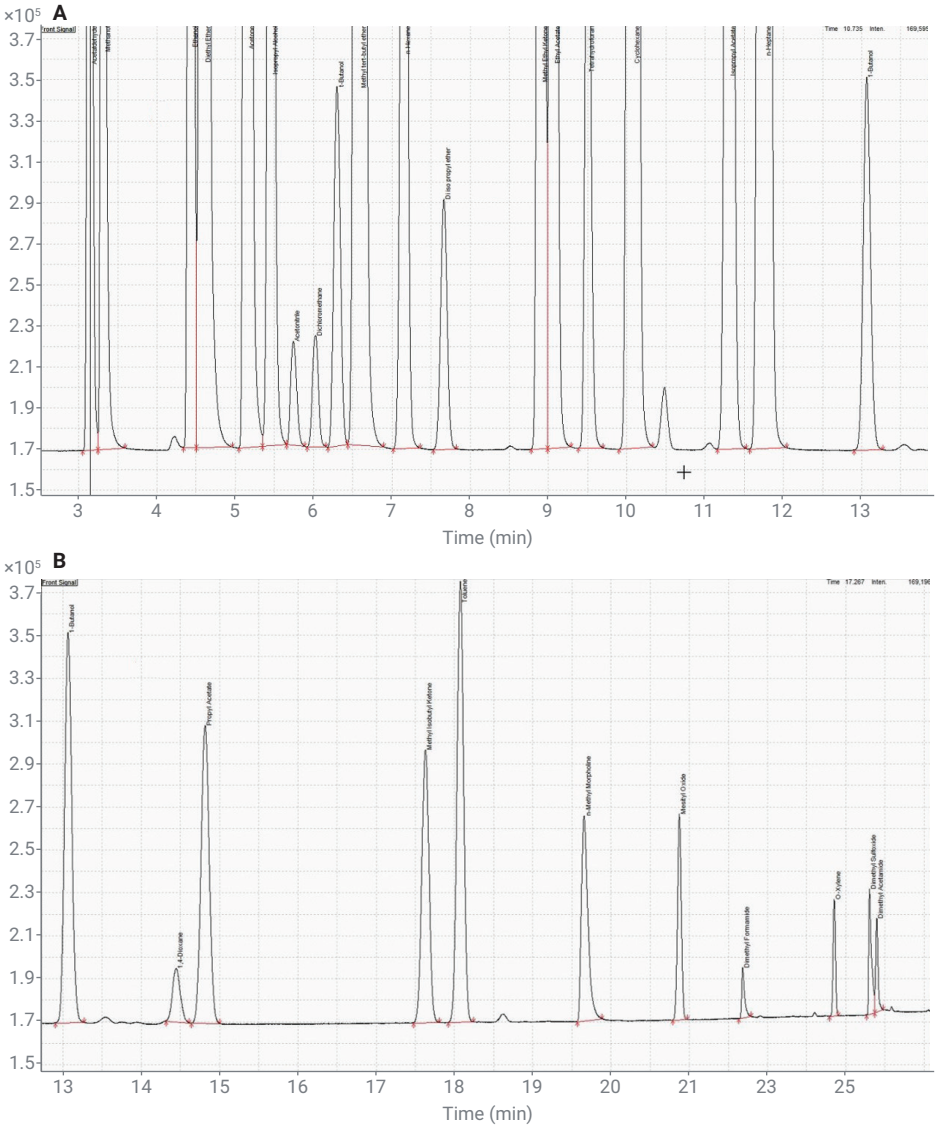

Figure 4. Separation of the impurities from (A) from RT 2.5 to 14 minutes and (B) 12.75 to 24 minutes.

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