

1 **Advanced GC Method for Comprehensive Residual Solvent Analysis:**
2 **Overcoming Co-elution with Orthogonal Columns and Quantification**
3 **by Mass Spectrometry**

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1 **Table S1: Summary of 40 solvents used for method development with Agilent GC-FID.**

Sr. No	Solvent name	CAS No.	ICH class	Permissible Limit (ppm)	Concentration used in study (ppm)
1	Methanol	67-56-1	Class 2	3000	3150
2	Acetonitrile	75-05-8	Class 2	410	455
3	Dichloromethane	75-09-2	Class 2	600	590
4	t-Butanol	75-65-0	Class 2	3500	3845
5	Hexane	110-54-3	Class 2	290	305
6	Tetrahydrofuran	109-99-9	Class 2	720	815
7	Cyclohexane	110-82-7	Class 2	3880	3945
8	1,4-Dioxane	123-91-1	Class 2	380	415
9	Toluene	108-88-3	Class 2	890	915
10	2-Hexanone	591-78-6	Class 2	50	49
11	Ethylene glycol	107-21-1	Class 2	620	635
12	Dimethylformamide	68-12-2	Class 2	880	910
13	p-Xylene	106-42-3	Class 2	2170	2280
14	Dimethylacetamide	127-19-5	Class 2	1090	1200
15	Ethanol	64-17-5	Class 3	5000	5142
16	Pentane	109-66-0	Class 3	5000	5125
17	Diethyl ether	60-29-7	Class 3	5000	5314
18	Acetone	67-64-1	Class 3	5000	4978
19	Isopropyl alcohol	67-63-0	Class 3	5000	5155
20	Methyl acetate	79-20-9	Class 3	5000	4995
21	t-Butyl methyl ether	1634-04-4	Class 3	5000	4955
22	1-Propanol	71-23-8	Class 3	5000	5245
23	Methylethylketone	78-93-3	Class 3	5000	5225
24	Ethyl acetate	141-78-6	Class 3	5000	5145
25	2-Methyl-1-propanol	78-83-1	Class 3	5000	4785
26	Isopropyl acetate	108-21-4	Class 3	5000	5120
27	2-Methyltetrahydrofuran	96-47-9	Class 3	5000	5450
28	Heptane	142-82-5	Class 3	5000	4750
29	1-Butanol	71-36-3	Class 3	5000	5120
30	3-Methyl-1-butanol	123-51-3	Class 3	5000	5145
31	1-Pentanol	71-41-0	Class 3	5000	5124
32	Butyl acetate*	123-86-4	Class 3	5000	5125
33	Dimethyl sulfoxide	67-68-5	Class 3	5000	4785
34	Iso-propyl ether	108-20-3	NA	1000*	1154
35	Methyl cyclopentane	96-37-7	NA	1000*	1045
36	t-Butyl acetate	540-88-5	NA	1000*	1060
37	2-Ethoxy propanol	19089-47-5	NA	1000*	1054
38	Cyclopentanone	120-92-3	NA	1000*	975
39	Ethylbenzene	100-41-4	NA	1000*	1005
40	o-Xylene	95-47-6	NA	1000*	1010

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3 NA - adequate toxicological data is not available as per ICH guidelines, and a limit of 1000* ppm was used for the method development
4 and validation study.

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1 **Table S2: Summary of 57 solvents used for method development with Agilent GC-FID and Thermo GC-FID-MS.**

Sr. No	Solvent	CAS no	ICH class	Permissible limit (ppm)	Concentration used in study (ppm)	Solvent polarity
1	Benzene	71-43-2	Class 1	2	2.1	HNP
2	Formamide	75-12-7	Class 1	220	245.3	HP
3	Methanol	67-56-1	Class 2	3000	3480	MP
4	1,2-Dichloroethene	156-59-2	Class 2	1870	1790	MP
5	Acetonitrile	75-05-8	Class 2	410	390	MP
6	Dichloromethane	75-09-2	Class 2	600	686	MP
7	Hexane	110-54-3	Class 2	290	263	HNP
8	Nitromethane	75-52-5	Class 2	50	59.3	MNP
9	Tetrahydrofuran	109-99-9	Class 2	720	733	MP
10	Trichloromethane	67-66-3	Class 2	60	58	MP
11	Cyclohexane	110-82-7	Class 2	3880	3993	HNP
12	2-Methoxyethanol	109-86-4	Class 2	50	56.6	PO
13	1,2-Dimethoxyethane	110-71-4	Class 2	100	123	MP
14	1,1,2-Trichloroethene	79-00-5	Class 2	80	76	MNP
15	1,4-Dioxane	123-91-1	Class 2	380	399	MP
16	Methyl isobutyl ketone	108-10-1	Class 2	4500	3602	MP
17	Pyridine	110-86-1	Class 2	200	162.6	PO
18	Toluene	108-88-3	Class 2	890	954	HNP
19	2-Hexanone	591-78-6	Class 2	50	62	MP
20	Ethylene glycol	107-21-1	Class 2	620	621	PO
21	Dimethylformamide	68-12-2	Class 2	880	1023	HP
22	Chlorobenzene	108-90-7	Class 2	360	356.6	MNP
23	p-Xylene	106-42-3	Class 2	2170	2080	HNP
24	Dimethylacetamide	127-19-5	Class 2	1090	1048	HP
25	Cumene	98-82-8	Class 2	70	86.6	HNP
26	Ethanol	64-17-5	Class 3	5000	5452	MP
27	Pentane	109-66-0	Class 3	5000	4962	HNP
28	Diethyl ether	60-29-7	Class 3	5000	5274	MP
29	Acetone	67-64-1	Class 3	5000	5364	MP
30	Isopropyl alcohol	67-63-0	Class 3	5000	5070	MP
31	Ethyl formate	109-94-4	Class 3	5000	5398	MP
32	Methyl acetate	79-20-9	Class 3	5000	5313	MP
33	t-Butanol	75-65-0	Class 3	3500	3345	PO
34	Methyl tert-butyl ether	1634-04-4	Class 3	5000	4835	MP
35	1-Propanol	71-23-8	Class 3	5000	5512	MP
36	Methyl ethyl ketone	78-93-3	Class 3	5000	4860	PO
37	Ethyl acetate	141-78-6	Class 3	5000	4866	MP
38	2-Butanol	78-92-2	Class 3	5000	5269	HP
39	2-Methyl-1-propanol	78-83-1	Class 3	5000	4963	MNP
40	Isopropyl acetate	108-21-4	Class 3	5000	5460	MP
41	2-methyl-tetrahydrofuran	96-47-9	Class 3	5000	5016	MP
42	Triethylamine	121-44-8	Class 3	5000	4661	NP
43	Heptane	142-82-5	Class 3	5000	5531	HNP
44	1-Butanol	71-36-3	Class 3	5000	5002	MP
45	Methylcyclohexane	108-87-2	Class 3	1180	1091	NP
46	n-Propylacetate	109-60-4	Class 3	5000	5556	MP
47	2-Ethoxyethanol	110-80-5	Class 3	160	199	PO
48	Cyclopentyl methyl ether	5614-37-9	Class 3	1500	1527	MP
49	3-Methyl-1-butanol	123-51-3	Class 3	5000	4742	PO
50	Isobutyl acetate	110-19-0	Class 3	5000	5266	MP
51	1-Pentanol	71-41-0	Class 3	5000	4926	MP
52	n-Butyl acetate	123-86-4	Class 3	5000	4820	MP
53	Dimethyl Sulfoxide	67-68-5	Class 3	5000	5022	HP
54	Anisole	100-66-3	Class 3	5000	4944	MP
55	Isopropyl ether	108-20-3	NA	1000*	933	NP
56	2,2-Dimethoxypropane	77-76-9	NA	1000*	1186	MP
57	Isooctane	540-84-1	NA	1000*	1401	HNP

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3 HNP- highly nonpolar, MNP - moderate nonpolar, P - nonpolar, PO - polar, MP - moderately polar, HP – highly polar.

4 NA - adequate toxicological data is not available as per ICH guidelines, and a limit of 1000* ppm was used for the method development
5 and validation study.

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1 Table S3a: Details of several trials performed to optimize the GC conditions for the separation of 40 solvents.

Trials	GC column flow rate optimization (ml/min)											
	Trial-1 (Figure-S1 to S4)			Trial-2 (Figure-S5)			Trial-3 (Figure-S6)			Trial-4 (Figure-S7)		
Instrument	Agilent 7890B GC system			Agilent 7890B GC system			Agilent 7890B GC system			Agilent 7890B GC system		
Column	VF-624 to HP-5 dual columns setup			VF-624 to HP-5 dual columns setup			VF-624 to HP-5 dual columns setup			VF-624 to HP-5 dual columns setup		
Carrier Gas	Helium			Helium			Helium			Helium		
Column flow	2.3 ml at constant flow of Helium			3.5 ml at constant flow of Helium			4.0 ml at constant flow of Helium			5.0 ml at constant flow of Helium		
Injection Volume	1 µl			1 µl			1 µl			1 µl		
Injection Mode	Split (Split ratio 20:1)			Split (Split ratio 20:1)			Split (Split ratio 20:1)			Split (Split ratio 20:1)		
GC Column	Rate (°C/min)	Temp. (°C)	Hold Time (Min)	Rate (°C/min)	Temp. (°C)	Hold Time (Min)	Rate (°C/min)	Temp. (°C)	Hold Time (Min)	Rate (°C/min)	Temp. (°C)	Hold Time (Min)
GC oven program	0	35	0.5	0	35	0.5	0	35	0.5	0	35	0.5
	10	150	2.5	10	150	2.5	10	150	2.5	10	150	2.5
	75	240	5.0	75	240	5.0	75	240	5	75	240	5.0
Injection Temperature	250 °C			250 °C			250 °C			250 °C		
Injection Volume	1 µl			1 µl			1 µl			1 µl		
Detector - FID	FID Conditions:			FID Conditions:			FID Conditions:			FID Conditions:		
	Temperature 300 ⁰ C			Temperature 300 ⁰ C			Temperature 300 ⁰ C			Temperature 300 ⁰ C		
	Hydrogen at 30 ml/min			Hydrogen at 30 ml/min			Hydrogen at 30 ml/min			Hydrogen at 30 ml/min		
	Air at 400 ml/min			Air at 400 ml/min			Air at 400 ml/min			Air at 400 ml/min		
Nitrogen Make up gas at 25 ml/min.			Nitrogen Make up gas at 25 ml/min.			Nitrogen Make up gas at 25 ml/min.			Nitrogen Make up gas at 25 ml/min.			

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1 Table S3b: Details of several trials performed to optimize the GC conditions for the separation of 40 solvents.

Trials	Temperature gradient optimization (Rate °C/min)								
	Trial-5 (Figure-S8)			Trial-6 (Figure-S9)			Trial-7 (Figure-S10)		
Instrument	Agilent GC system			Agilent GC system			Agilent GC system		
Column	VF-624 to HP-5 dual columns setup			VF-624 to HP-5 dual columns setup			VF-624 to HP-5 dual columns setup		
Carrier Gas	Helium			Helium			Helium		
Column flow	5.0 ml at constant flow of Helium			5.0 ml at constant flow of Helium			5.0 ml at constant flow of Helium		
Injection Volume	1µl			1µl			1µl		
Injection Mode	Split (Split ratio 20:1)			Split (Split ratio 20:1)			Split (Split ratio 20:1)		
GC Column	Rate (°C/min)	Temp. (°C)	Hold Time (Min)	Rate (°C/min)	Temp. (°C)	Hold Time (Min)	Rate (°C/min)	Temp. (°C)	Hold Time (Min)
Oven temperature gradient program	0	40	0.5	0	50	5.0	0	40	5.0
	10	90	1.0	3	65	1.0	3	48	0.5
	10	115	1.0	7	115	1.0	5	65	0.0
	10	125	1.0	10	125	1.0	10	75	0.5
	5	135	1.0	5	135	1.0	5	80	1.0
	10	150	1.0	10	150	1.0	10	95	1.0
	70	240	5.0	70	240	5.0	20	115	5.0
							50	240	5.0
Injection Temperature	250 °C			250 °C			250 °C		
Injection Volume	1µl			1µl			1µl		
Detector-FID	FID Conditions:			FID Conditions:			FID Conditions:		
	Temperature 300 °C			Temperature 300 °C			Temperature 300 °C		
	Hydrogen at 30 ml/min			Hydrogen at 30 ml/min			Hydrogen at 30 ml/min		
	Air at 400 ml/min			Air at 400 ml/min			Air at 400 ml/min		
Nitrogen Make up gas at 25 ml/min.			Nitrogen Make up gas at 25 ml/min.			Nitrogen Make up gas at 25 ml/min.			

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1 Table S4: Summary table of solvent retention times in Figures S1–S4 and resolution status.

Sr. No	VF 624 using Agilent GC-FID (Figure-S1)		HP-5 using Agilent GC-FID (Figure-S2)		Dual (VF-624 to HP-5) using Agilent GC-FID (Figure-S3)		Dual (HP-5 to VF-624) using Agilent GC-FID (Figure-S4)	
	Peak Name	RT (min)	Peak Name	RT (min)	Peak Name	RT (min)	Peak Name	RT (min)
1	Methanol	2.67	Methanol	1.74	Methanol	7.66	Methanol	7.28
2	Pentane	3.46	Ethanol	2.07	Ethanol	8.79	Ethanol	8.12
3	Ethanol	3.55	Acetone	2.35	Pentane	8.86	Isopropyl alcohol	8.76
4	Diethyl ether	3.71	Acetonitrile	2.38	Diethyl ether	9.12	Acetone	8.77
5	Acetone	4.06	Isopropyl alcohol	2.42	Acetone	9.45	Diethyl ether	8.77
6	Isopropyl alcohol	4.23	Diethyl ether	2.52	Isopropyl alcohol	9.56	Acetonitrile	8.85
7	Acetonitrile	4.41	1-Butanol	2.72	Acetonitrile	9.79	t-Butanol	9.25
8	Methyl acetate	4.45	Methyl acetate	2.80	Methyl acetate	9.90	Methyl acetate	9.29
9	Dichloromethane	4.62	Dichloromethane	2.87	Dichloromethane	10.01	Dichloromethane	9.46
10	t-Butanol	4.73	1-Propanol	3.17	t-Butanol	10.11	1-Propanol	9.87
11	t-Butyl methyl ether	4.92	t-Butyl methyl ether	3.35	t-Butyl methyl ether	10.47	t-Butyl methyl ether	9.96
12	Hexane	5.25	Methylethylketone	3.78	1-Propanol	10.85	Hexane	10.46
13	Iso-propyl ether	5.48	Hexane	3.80	Iso-propyl ether	10.85	Iso-propyl ether	10.51
14	1-Propanol	5.48	Iso-propyl ether	3.90	Hexane	11.00	Methylethylketone	10.65
15	Methyl cyclopentane	5.93	Ethyl acetate	4.10	Methylethylketone	11.55	Ethyl acetate	10.84
16	Methylethylketone	6.04	Cyclohexane	4.32	Ethyl acetate	11.55	Methyl cyclopentane	11.20
17	Ethyl acetate	6.08	Tetrahydrofuran	4.38	Methyl cyclopentane	11.63	Tetrahydrofuran	11.29
18	Tetrahydrofuran	6.31	Isopropyl acetate	4.98	Tetrahydrofuran	11.95	Isopropyl acetate	11.75
19	Cyclohexane	6.66	t-Butanol	5.02	2-Methyl-1-propanol	12.24	1-Butanol	11.90
20	2-Methyl-1-propanol	6.84	2-Methyl tetrahydrofuran	5.15	Cyclohexane	12.41	Cyclohexane	11.94
21	Isopropyl acetate	7.01	Methyl cyclopentane	5.67	Isopropyl acetate	12.48	2-Methyl tetrahydrofuran	12.08
22	2-Methyl tetrahydrofuran	7.10	t-Butyl acetate	5.75	Heptane	12.75	Heptane	12.43
23	Heptane	7.26	1,4-Dioxane	5.84	2-Methyl tetrahydrofuran	12.89	t-Butyl acetate	12.56
24	1-Butanol	7.53	Butyl acetate	6.31	n-Butanol	12.96	1,4-Dioxane	12.88
25	t-Butyl acetate	7.75	3-Methyl-1-butanol	6.78	t-Butyl acetate	13.29	3-Methyl-1-butanol	13.35
26	1,4-Dioxane	7.99	Toluene	6.79	1,4-Dioxane	13.68	Dimethylacetamide	13.45
27	2-Ethoxy propanol	8.85	2-Methyl-1-propanol	6.90	2-Ethoxy propanol	14.42	Ethylene glycol	13.54
28	Toluene	9.02	1-Pentanol	6.90	3-Methyl-1-butanol	14.49	Butyl acetate	13.72
29	3-Methyl-1-butanol	9.40	Pentane	6.93	Ethylene glycol	14.71	2-Methyl-1-propanol	14.03
30	1-Pentanol	9.40	2-Ethoxy propanol	6.99	Toluene	14.89	1-Pentanol	14.05
31	2-Hexanone	9.47	Dimethylformamide	7.16	1-Pentanol	14.98	Pentane	14.06
32	Butyl acetate	9.60	Ethylene glycol	7.24	2-Hexanone	15.35	2-Ethoxy propanol	14.21
33	Ethylene glycol	9.71	2-Hexanone	7.33	Butyl acetate	15.50	Toluene	14.29
34	Cyclopentanone	10.17	Cyclopentanone	7.38	Cyclopentanone	15.67	2-Hexanone	14.63
35	Dimethylformamide	10.68	Dimethyl sulfoxide	8.07	Dimethylformamide	15.74	Dimethylformamide	14.79
36	Ethylbenzene	10.84	Heptane	8.46	Ethylbenzene	16.45	Cyclopentanone	14.92
37	p-Xylene	11.27	Ethylbenzene	8.67	p-Xylene	16.60	Dimethyl sulfoxide	15.77
38	o-Xylene	11.42	Dimethylacetamide	8.71	Dimethyl sulfoxide	16.97	Ethylbenzene	15.87
39	Dimethyl sulfoxide	11.54	p-Xylene	8.80	o-Xylene	17.08	p-Xylene	15.98
40	Dimethylacetamide	11.60	o-Xylene	9.20	Dimethylacetamide	17.26	o-Xylene	16.38

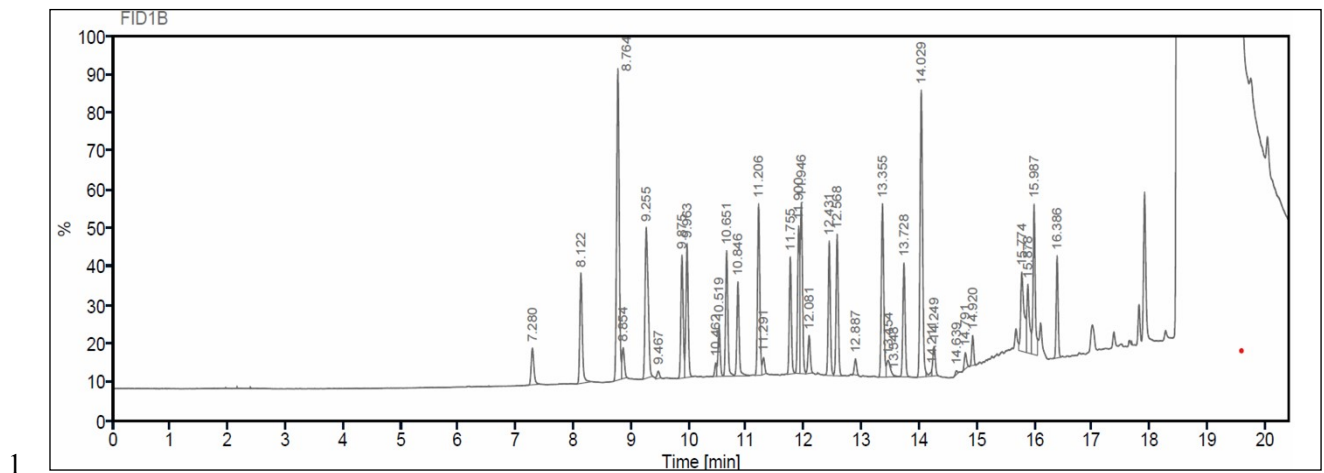
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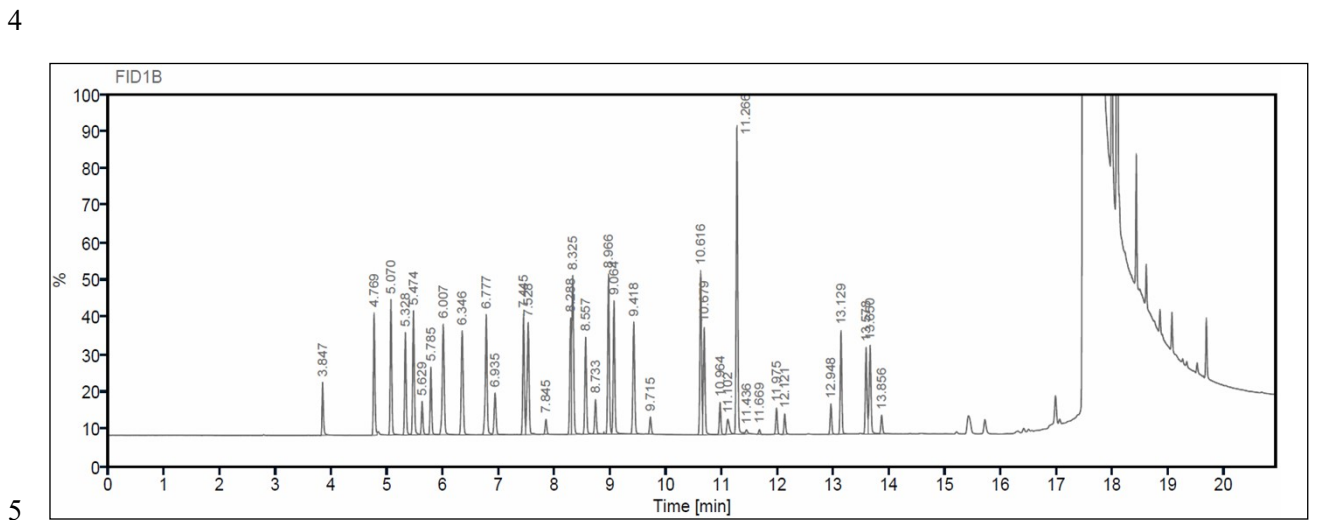
4 RT – Retention time.

5 Peak resolution status: Black colour solvents are well separated (resolution > 1.5), Blue colour solvents are partially separated (resolution between 1.0 to 1.5), and Red colour solvents are merged (not separated, resolution < 1.0).

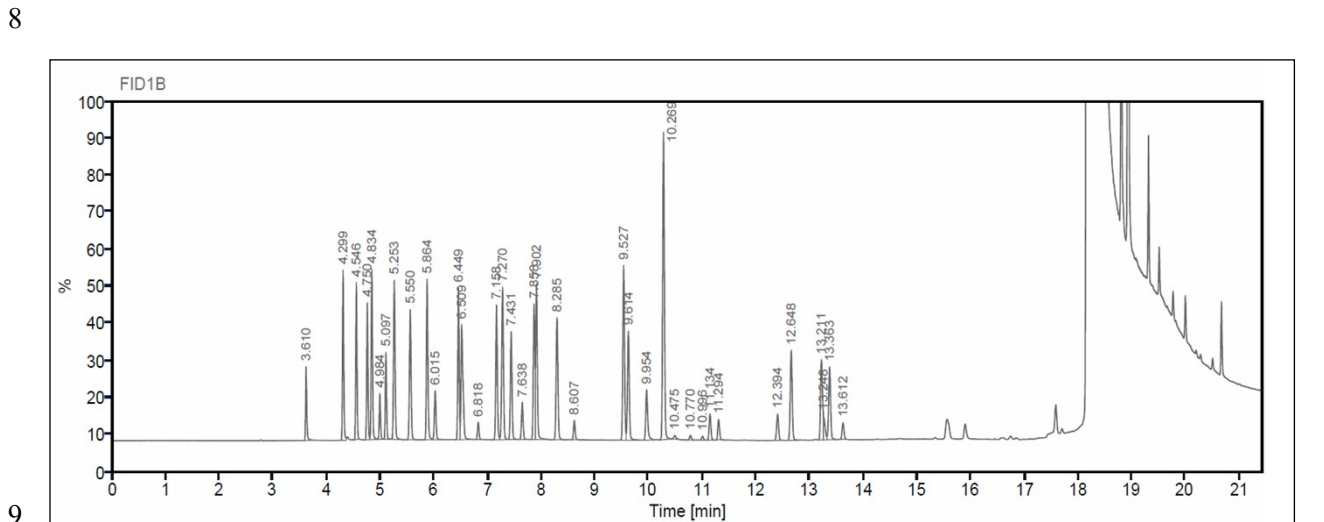
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 2 Figure S4: Chromatogram of 40 solvents on a dual-column configuration, HP-5 to VF-624 with an Agilent GC-FID instrument (Trial-
 3 1, Table S3a).



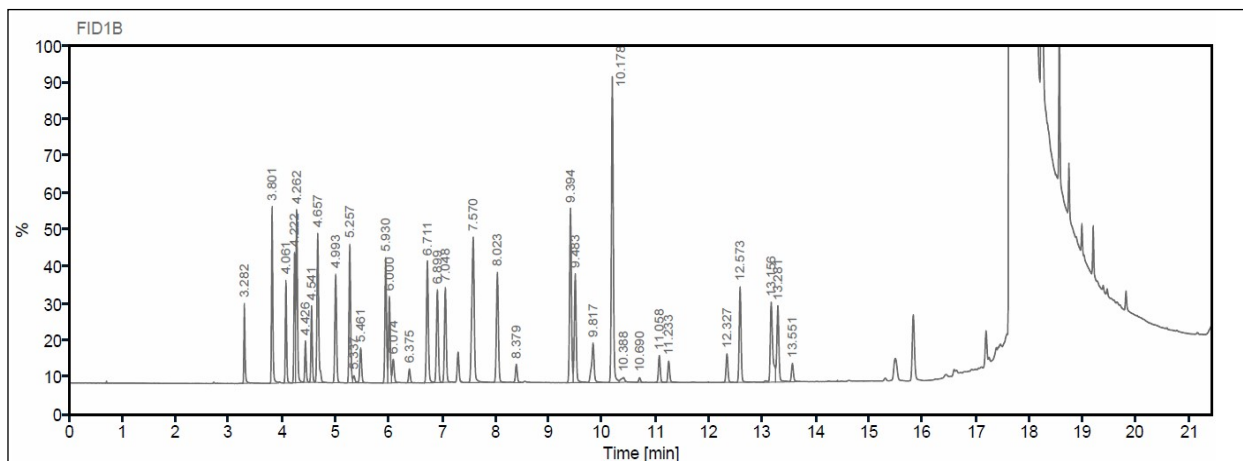
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 6 Figure S5: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument, trial-1
 7 with flow rate of 3.5ml/min. (Trial-2, Table S3a).



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 10 Figure S6: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument with
 11 flow rate of 4.0ml/min (Trial-3, Table S3a).

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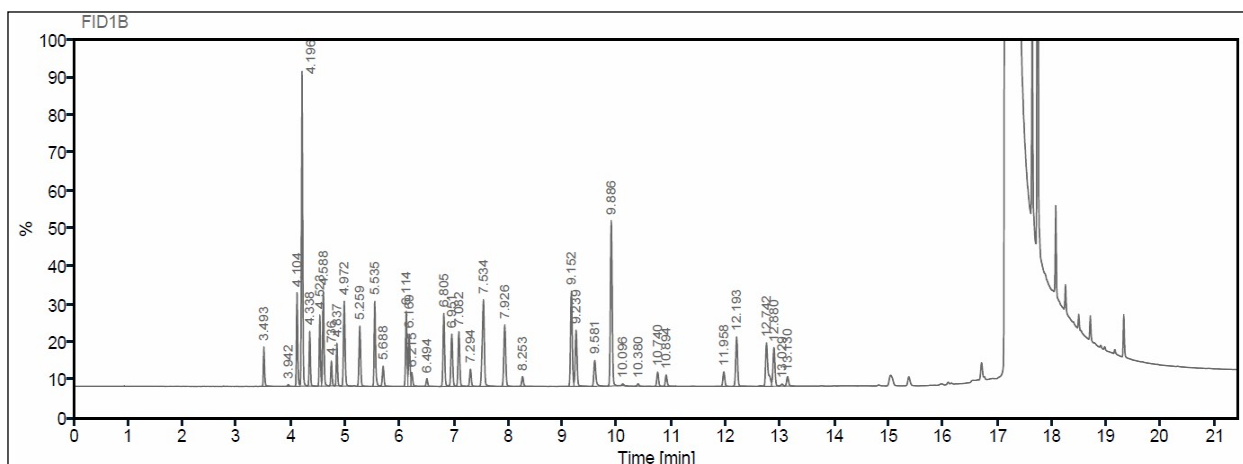
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2 Figure S7: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument with
3 flow rate of 5.0ml/min (Trial-4, Table S3a).

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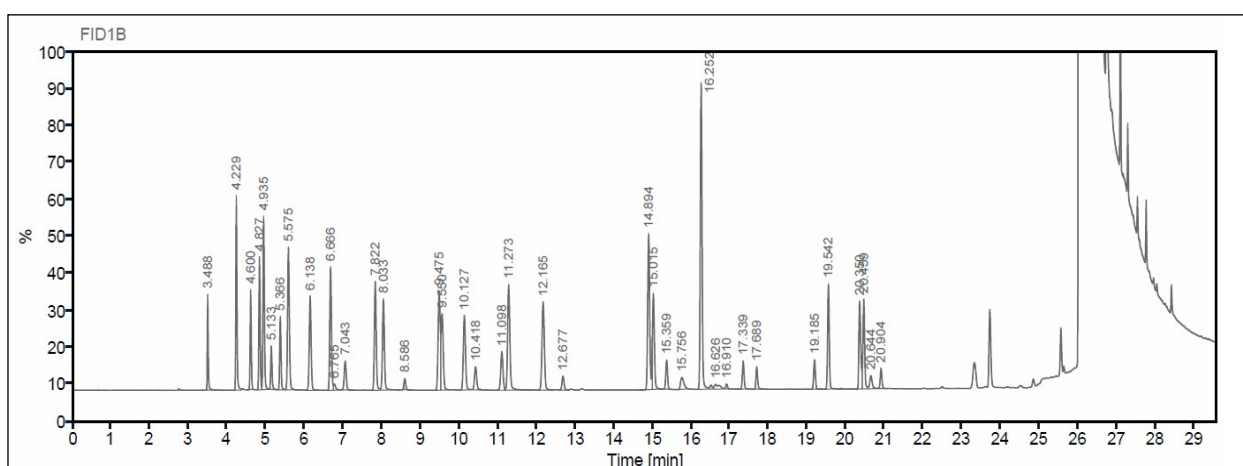
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6 Figure S8: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument with
7 modified oven program (Trial-5, Table S3b).

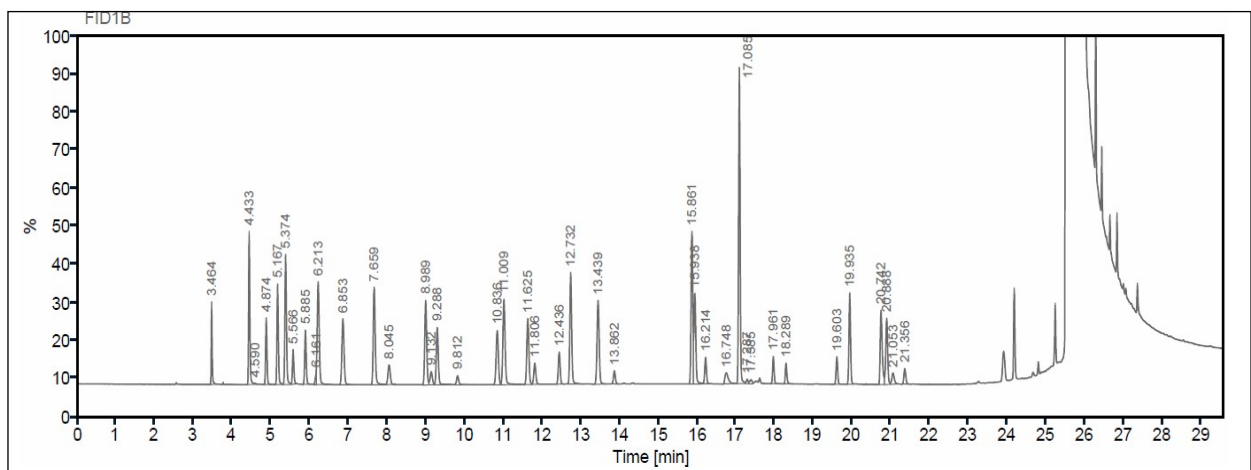
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10 Figure S9: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument with
11 modified oven program (Trial-6, Table S3b).

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 2 Figure S10: Chromatogram of 40 solvents on a dual-column configuration, VF-624 to HP5 with an Agilent GC-FID instrument with
 3 final optimized oven program (Trial-7, Table S3b).

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1 **Table S5: Summary table of solvent retention times in Figures S10 and resolution status.**

VF-624 to HP-5 using Agilent GC-FID - Optimized method (Trial 7 Table S3b).		
Sr. No	Peak Name	RT (min)
1	Methanol	3.46
2	Ethanol	4.43
3	Pentane	4.59
4	Diethyl ether	4.87
5	Acetone	5.16
6	Isopropyl alcohol	5.37
7	Acetonitrile	5.56
8	Methyl acetate	5.88
9	Dichloromethane	6.16
10	t-Butanol	6.21
11	t-Butyl methyl ether	6.85
12	1-Propanol	7.66
13	Hexane	8.04
14	Isopropyl ether	8.99
15	Methyl cyclopentane	9.13
16	Methylethylketone	9.29
17	Tetrahydrofuran	9.81
18	Ethyl acetate	10.84
19	Cyclohexane	11.01
20	2-Methyl-1-propanol	11.63
21	t-Butyl acetate	11.81
22	2-Methyl tetrahydrofuran	12.44
23	Heptane	12.73
24	1-Butanol	13.44
25	1,4-Dioxane	13.86
26	Isopropyl acetate	15.86
27	Butyl acetate	15.94
28	Toluene	16.21
29	1-Pentanol	16.75
30	3-Methyl-1-butanol	17.08
31	2-Ethoxy propanol	17.29
32	2-Hexanone	17.38
33	Ethylene glycol	17.96
34	Cyclopentanone	18.29
35	Dimethylformamide	19.60
36	Ethylbenzene	19.93
37	p-Xylene	20.74
38	o-Xylene	20.89
39	Dimethyl sulfoxide	21.05
40	Dimethylacetamide	21.36

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3 Peak resolution status: Black colour solvents are well separated (resolution >1.5), and Blue colour solvents are partially separated
4 (resolution between 1.0 to 1.5).

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1 Table S6: Details of optimized method parameters used with Thermo GC-FID-MS for the separation of 57 solvents.

Trials	Temperature gradient optimization (Rate °C/min)		
	Trail-8 (Figure-2, and Figure S11 to S15)		
Instrument	Thermo scientific GC		
Column	VF-624 to HP-5 dual columns setup		
Carrier Gas	Helium		
Column flow	5.0 ml at constant flow of Helium		
Injection Volume	1µl		
Injection Mode	Split (Split ratio 35:1)		
GC Column	Rate (°C/min)	Temp. (°C)	Hold Time (Min)
Oven temperature gradient program	0	40	5.0
	2	45	2.0
	3	48	0.5
	5	65	0.0
	10	70	1.0
	5	80	0.0
	10	95	1.0
	20	115	5.0
50	240	5.0	
Injection Temperature	250 °C		
Injection Volume	1µl		
Detector- FID	FID Conditions:		
	Temperature 300 °C		
	Hydrogen at 30 ml/min		
	Air at 400 ml/min		
	Helium Make up gas at 25 ml/min.		
Detector - MS	MS - Scan Mode:		
	Interface Temperature is 280 °C		
	Ion Source Temperature is 250 °C		
	Scan Range: m/z 31-200		
	Acquisition Mode: Full Scan		

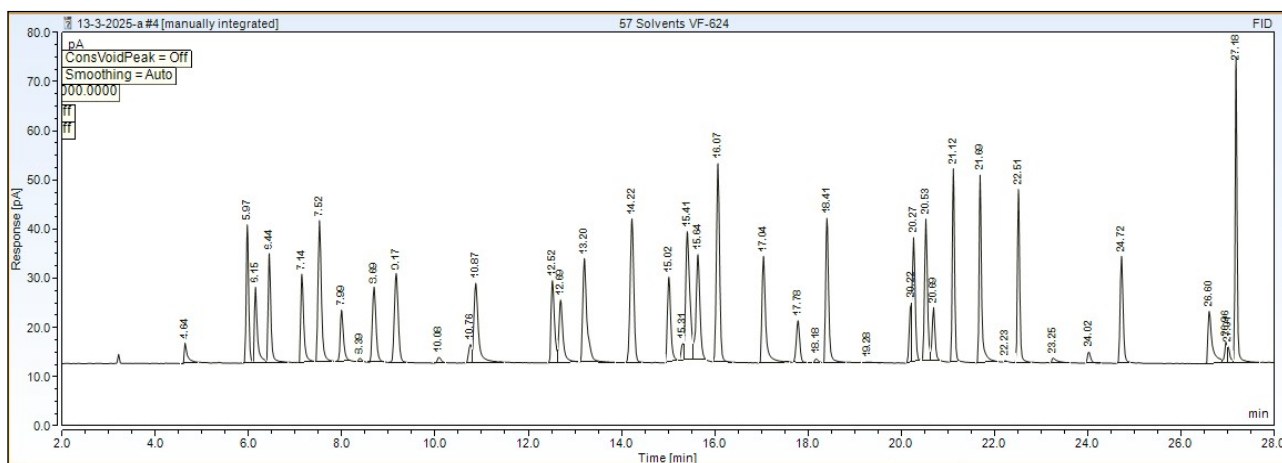
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1 Table S7: Summary table of solvent retention times in Figures S11–S15, Figure 2, and Figure 3 with their resolution status.

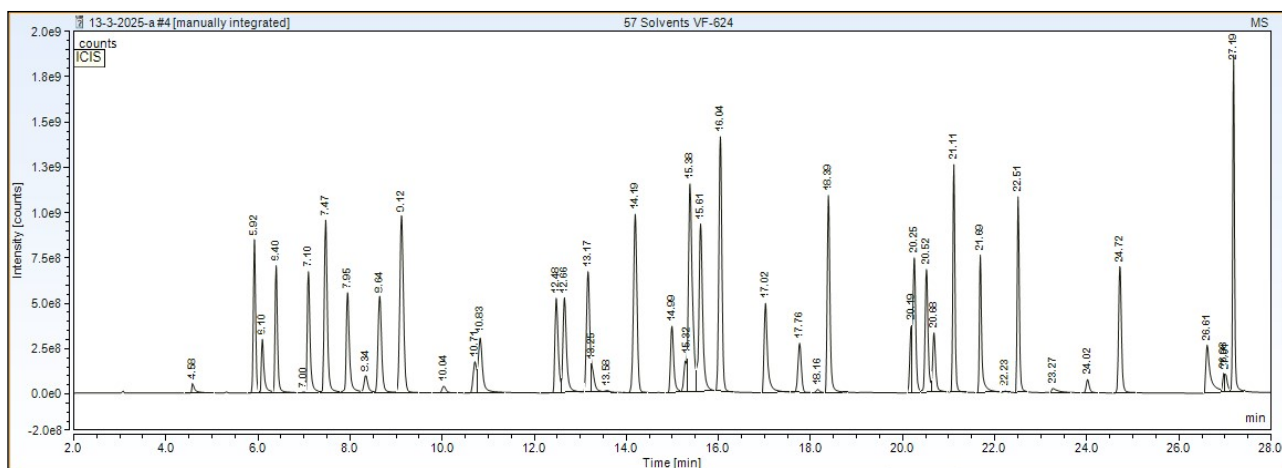
Sr. No	VF 624 using GC-FID, and MS (scan) detectors (Figure-S11, and S12)		HP 5 using FID, and MS (scan) detectors (Figure-S13, and 14)		Dual Column, VF-624 to HP-5 using FID, MS (SIM), and MS (scan) detectors (Figure-2, 3, and S15)	
	Peak Name	RT (Min)	Peak Name	RT (Min)	Peak Name	RT (Min)
1	Methanol	4.64	Methanol	4.53	Methanol	5.22
2	Pentane	5.97	Ethanol	5.23	Ethanol	6.65
3	Ethanol	6.15	Acetonitrile	5.84	Pentane	6.87
4	Ethyl ether	6.44	Isopropyl alcohol	5.85	Ethyl ether	7.27
5	1,2-Dichloroethene	7.02	Acetone	5.86	1,2-Dichloroethene	7.67
6	Acetone	7.14	Pentane	5.86	Acetone	7.67
7	Isopropyl alcohol	7.52	Ethyl ether	6.19	Isopropyl alcohol	7.99
8	Ethylformate	7.52	Ethylformate	6.46	Methyl acetate	8.68
9	Acetonitrile	7.91	t-Butanol	6.59	t-Butanol	9.07
10	Methyl acetate	7.99	Methyl acetate	6.77	Dichloromethane	9.15
11	Dichloromethane	8.39	Dichloromethane	6.92	Ethylformate	9.21
12	t-Butanol	8.69	1-Propanol	7.58	Acetonitrile	9.21
13	Methyl tert-butyl ether	9.17	Nitromethane	7.64	Methyl tert-butyl ether	10.07
14	Hexane	10.08	Methyl tert-butyl ether	8.01	Hexane	11.22
15	Isopropyl ether	10.75	Hexane	8.87	1-Propanol	11.22
16	1-Propanol	10.87	Methyl ethyl ketone	9.09	Isopropyl ether	11.75
17	Methyl ethyl ketone	12.52	2-Butanol	9.25	Nitromethane	12.42
18	Nitromethane	12.69	Isopropyl ether	9.38	Methyl ethyl ketone	12.98
19	2-Butanol	13.20	Ethyl acetate	9.99	Ethyl acetate	13.37
20	Tetrahydrofuran	13.28	Trichloromethane	10.08	2-Butanol	13.64
21	Trichloromethane	13.60	2-Methyl-1-propanol	10.62	Tetrahydrofuran	14.09
22	2,2-Dimethoxypropane	14.00	Tetrahydrofuran	10.86	Trichloromethane	14.29
23	Cyclohexane	14.22	2-Methoxyethanol	10.91	2,2-Dimethoxypropane	15.18
24	2-Methyl-1-propanol	15.02	1,2-Dichloroethene	11.98	Cyclohexane	15.35
25	Benzene	15.12	2,2-Dimethoxypropane	12.24	2-Methyl-1-propanol	15.55
26	1,2-Dimethoxyethane	15.17	1,2-Dimethoxyethane	12.27	2-Methoxyethanol	15.55
27	2-Methoxyethanol	15.31	1-Butanol	12.46	Benzene	15.89
28	Isopropyl acetate	15.39	Benzene	12.62	1,2-Dimethoxyethane	16.07
29	Isooctane	15.41	Cyclohexane	12.65	Isopropyl acetate	16.29
30	2-Methyl tetrahydrofuran	15.53	Isopropyl acetate	12.71	2-Methyl tetrahydrofuran	16.69
31	Triethylamine	15.64	2-Methyl tetrahydrofuran	13.21	Triethylamine	16.7
32	Heptane	16.07	Isooctane	14.04	Isooctane	16.76
33	Ethyl acetate	17.04	Triethylamine	14.16	Heptane	17.35
34	1-Butanol	17.04	Heptane	14.69	1-Butanol	17.74
35	1,1,2-Trichloroethene	17.08	1,1,2-Trichloroethene	14.88	1,1,2-Trichloroethene	18.22
36	Methylcyclohexane	17.78	1,4-Dioxane	15.22	Methylcyclohexane	19.04
37	1,4-Dioxane	18.18	n-Propylacetate	15.51	1,4-Dioxane	19.04
38	n-Propylacetate	18.41	2-Ethoxyethanol	15.51	3-Methyl-1-butanol	19.09
39	2-Ethoxyethanol	19.28	Methylcyclohexane	16.12	n-Propylacetate	19.34
40	Cyclopentyl methyl ether	20.22	3-Methyl-1-butanol	16.60	2-Ethoxyethanol	19.95
41	Methylisobutylketone	20.26	Methylisobutylketone	16.94	Methylisobutylketone	21.24
42	Pyridine	20.45	Pyridine	17.43	Pyridine	21.34
43	3-Methyl-1-butanol	20.53	1-Pentanol	18.12	Cyclopentyl methyl ether	21.43
44	Toluene	20.69	Ethylene glycol	18.32	Toluene	21.81
45	Isobutyl acetate	21.12	Cyclopentyl methyl ether	18.49	Isobutyl acetate	22.16
46	1-Pentanol	21.69	Toluene	18.50	1-Pentanol	22.73
47	2-Hexanone	22.23	Isobutyl acetate	18.69	2-Hexanone	23.39
48	Ethylene glycol	22.43	Formamide	18.75	Ethylene glycol	23.53
49	n-Butyl acetate	22.51	Dimethylformamide	19.10	n-Butyl acetate	23.84
50	Dimethylformamide	23.25	2-Hexanone	19.42	Formamide	23.96
51	Formamide	24.00	n-Butyl acetate	20.44	Dimethylformamide	24.25
52	Chlorobenzene	24.02	Dimethyl sulfoxide	21.36	Chlorobenzene	25.62
53	p-Xylene	24.73	Chlorobenzene	21.85	p-Xylene	26.49
54	Dimethyl sulfoxide	26.61	Dimethylacetamide	22.58	Dimethyl sulfoxide	27.4
55	Dimethylacetamide	26.97	p-Xylene	22.64	Dimethylacetamide	27.81
56	Cumene	27.01	Anisole	24.38	Cumene	28.14
57	Anisole	27.18	Cumene	24.73	Anisole	28.24

2 Peak resolution status: Black colour solvents are well separated (resolution > 1.5), Blue colour solvents are partially separated (resolution
3 between 1.0 to 1.5), and Red colour solvents are merged (not separated, resolution <1.0).



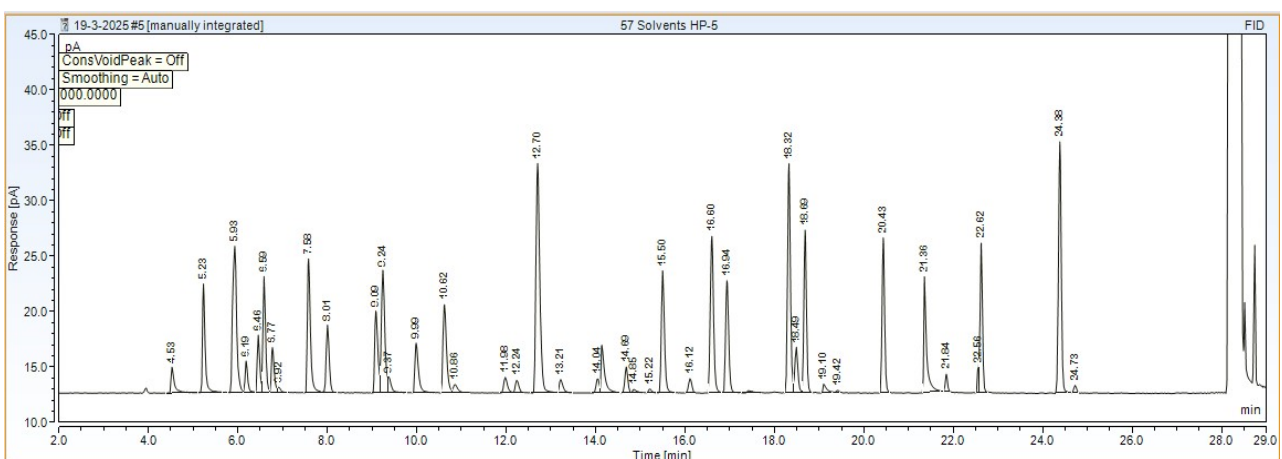
1
 2 Figure S11: FID detector chromatogram of 57 solvents on a VF-624 with a Thermo GC-FID-MS instrument using the final optimized
 3 method (Trial-8, Table S6).

4



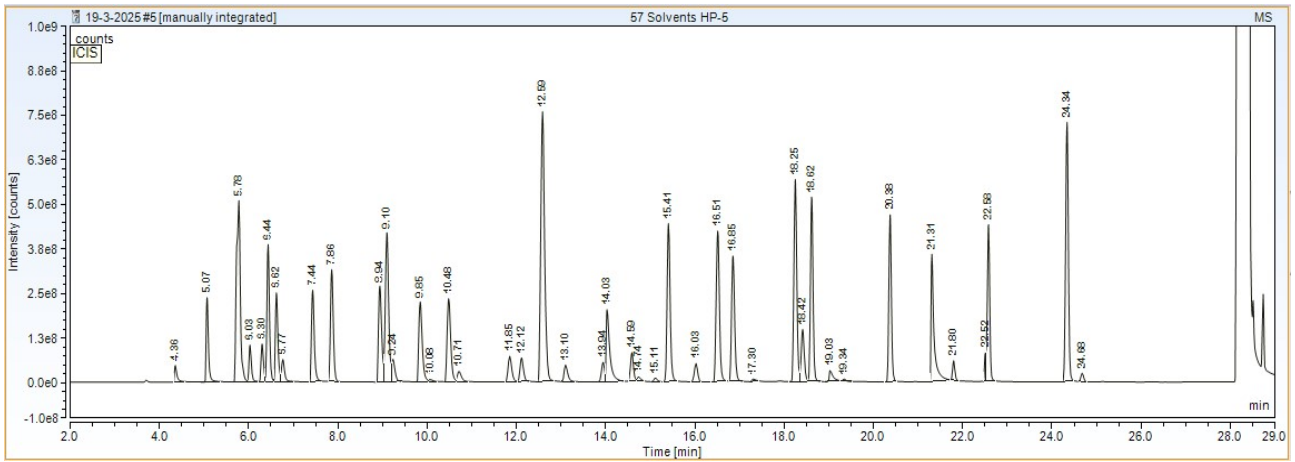
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 6 Figure S12: MS (scan mode) chromatogram of 57 solvents on a VF-624 with a Thermo GC-FID-MS instrument using the final optimized
 7 method (Trial-8, Table S6).

8

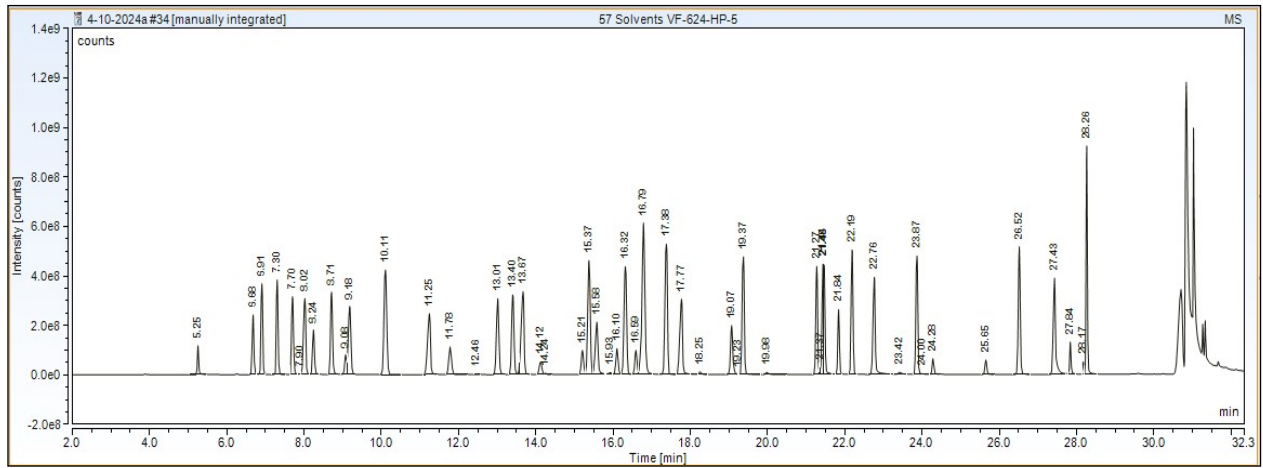


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 10 Figure S13: FID detector chromatogram of 57 solvents on an HP-5 with a Thermo GC-FID-MS instrument using the final optimized
 11 method (Trial-8, Table S6).

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1
 2 Figure S14: MS (scan mode) chromatogram of 57 solvents on a HP-5 with a Thermo GC-FID-MS instrument using the final optimized
 3 method (Trial-8, Table S6).
 4



5
 6 Figure S15: MS (scan mode) chromatogram of 57 solvents on a dual-column configuration, VF-624 to HP5 with a Thermo GC-FID-MS
 7 instrument using the final optimized method (Trial-8, Table S6).
 8

1 Table S8: Optimised parameters of GC-MS, SIM mode used for validation study (Figure 3, and 4).
2

Sr. No	Peak Name	RT (min)	Window (min)	Selected ion	Molecular weight
1	Methanol	5.25	+1.0 to -1.0	31.0	32.04
2	Ethanol	6.68	+0.5 to -0.5	45.0	46.07
3	Pentane	6.91	+0.5 to -0.5	43.0	72.15
4	Ethyl ether	7.31	+0.5 to -0.5	74.0	74.12
5	Acetone	7.71	+0.5 to -0.5	43.0	58.08
6	1,1-Dichloroethene	7.71	+0.5 to -0.5	96.0	96.94
7	Isopropyl alcohol	8.02	+0.5 to -0.5	45.0	60.10
8	Ethylformate	8.24	+0.5 to -0.5	45.0	74.08
9	Acetonitrile	8.25	+0.5 to -0.5	41.0	41.05
10	Methyl acetate	8.71	+0.5 to -0.5	43.0	74.08
11	Dichloromethane	9.08	+0.5 to -0.5	84.0	84.93
12	t-Butanol	9.18	+0.5 to -0.5	59.0	74.12
13	Methyl tert-butyl ether	10.11	+0.5 to -0.5	73.0	88.15
14	Hexane	11.23	+0.5 to -0.5	57.0	86.18
15	1-Propanol	11.23	+0.5 to -0.5	59.0	60.10
16	Iso propyl ether	11.78	+0.5 to -0.5	87.0	102.18
17	Nitromethane	12.45	+0.5 to -0.5	61.0	61.04
18	Methyl ethyl ketone	13.01	+0.5 to -0.5	72.0	72.11
19	Ethyl acetate	13.39	+0.5 to -0.5	70.0	88.11
20	2-Butanol	13.65	+1.0 to -1.0	59.0	74.12
21	Tetrahydrofuran	14.12	+0.5 to -0.5	72.0	72.11
22	Trichloromethane	14.24	+0.5 to -0.5	84.0	119.38
23	2,2-Dimethoxy propane	15.20	+0.5 to -0.5	89.0	104.15
24	Cyclohexane	15.37	+0.5 to -0.5	84.0	84.16
25	2-Methyl-1-propanol	15.37	+0.5 to -0.5	43.0	74.12
26	2-Methoxy ethanol	15.58	+0.5 to -0.5	45.0	76.09
27	1,2-Dimethoxy ethane	16.09	+0.5 to -0.5	60.0	90.12
28	Benzene	16.09	+0.5 to -0.5	78.0	78.11
29	Isopropyl acetate	16.31	+0.5 to -0.5	61.0	102.13
30	2-Methyl tetrahydrofuran	16.59	+0.5 to -0.5	71.1	86.13
31	Iso octane	16.73	+0.5 to -0.5	57.1	114.23
32	Triethylamine	16.78	+0.5 to -0.5	101.0	101.19
33	Heptane	17.36	+0.5 to -0.5	71.1	100.23
34	1-Butanol	17.76	+0.5 to -0.5	56.1	74.12
35	Trichloroethylene	18.25	+0.5 to -0.5	130.0	131.39
36	Methylcyclohexane	19.07	+0.5 to -0.5	83.0	98.19
37	1,4-Dioxane	19.11	+0.5 to -0.5	88.0	88.11
38	n-Propylacetate	19.36	+0.5 to -0.5	61.0	102.13
39	2-Ethoxyethanol	19.98	+0.5 to -0.5	72.1	90.12
40	Pyridine	21.26	+0.5 to -0.5	79.1	79.10
41	Methylisobutylketone	21.27	+0.5 to -0.5	58.1	100.16
42	Cyclopentyl methyl ether	21.27	+0.5 to -0.5	71.0	100.16
43	3-Methyl-1-butanol	21.46	+0.5 to -0.5	70.1	88.15
44	Toluene	21.83	+0.5 to -0.5	92.0	92.14
45	Iso butyl acetate	22.18	+0.5 to -0.5	56.1	116.16
46	1-Pentanol	22.75	+0.5 to -0.5	70.1	88.15
47	2-Hexanone	23.40	+0.5 to -0.5	58.1	100.16
48	Ethylene glycol	23.58	+0.5 to -0.5	43.0	62.07
49	n-Butyl acetate	23.86	+0.5 to -0.5	56.1	116.16
50	Formamide	23.99	+1.0 to -1.0	45.0	45.04
51	Dimethylformamide	24.28	+0.5 to -0.5	73.0	73.09
52	Chlorobenzene	25.65	+0.5 to -0.5	112.0	112.56
53	p-Xylene	26.52	+0.5 to -0.5	106.0	106.17
54	Dimethyl sulfoxide	27.41	+2.5 to -2.5	78.0	78.13
55	Dimethylacetamide	27.83	+0.5 to -0.5	87.0	87.12
56	Cumene	28.17	+0.5 to -0.5	120.0	120.19
57	Anisole	28.26	+0.5 to -0.5	108.0	108.14

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1 Table S9: Recovery results for Verapamil Hydrochloride (API), and Calaptin 120SR tablet.

2

Sr. No	Peak Name	RT (min)	Verapamil-Recovery			Calaptin 120SR-Recovery		
			70%	110%	150%	70%	110%	150%
1	Methanol	5.26	112.50	95.36	101.92	82.78	98.06	91.06
2	Ethanol	6.67	107.66	106.42	107.56	83.21	97.63	88.10
3	Pentane	6.89	98.53	109.69	98.78	95.74	94.59	96.54
4	Ethyl ether	7.29	87.34	95.69	103.09	84.42	83.99	92.53
5	Acetone	7.67	96.29	87.12	102.98	96.47	95.65	87.20
6	1,1-Dichloroethene	7.98	101.15	94.97	88.48	88.71	103.21	92.03
7	Isopropyl alcohol	7.98	95.38	95.26	81.68	88.78	103.16	91.95
8	Ethyl formate	8.20	91.50	89.08	81.39	93.93	94.65	87.43
9	Acetonitrile	8.24	95.41	95.87	96.33	85.31	98.90	93.23
10	Methyl acetate	8.68	104.93	86.60	99.56	98.15	89.56	90.40
11	Dichloromethane	9.03	93.11	93.91	96.16	96.00	89.77	93.68
12	t-Butanol	9.14	108.26	94.51	96.33	85.93	104.24	85.30
13	MTBE	10.06	103.89	85.11	102.89	102.17	94.13	87.98
14	1-propanol	11.16	99.66	97.07	96.78	84.91	89.48	93.71
15	Hexane	11.17	99.06	97.25	101.14	100.10	99.94	88.37
16	isopropyl ether	11.72	96.82	84.50	98.60	98.52	84.63	94.01
17	Nitromethane	12.48	100.72	94.28	93.43	100.96	96.80	89.95
18	Methyl ethyl ketone	12.93	100.26	90.96	104.13	85.80	93.78	89.31
19	Ethyl acetate	13.33	88.78	90.10	103.75	83.77	92.40	89.93
20	2-Butanol	13.57	108.92	94.77	91.64	86.00	102.37	87.32
21	THF	14.05	86.91	85.46	96.30	91.66	92.36	91.03
22	Trichloro methane	14.15	98.88	95.24	108.95	84.68	98.37	89.03
23	2,2-Dimethoxy propane	15.14	103.21	89.19	101.10	84.9	94.14	89.02
24	cyclohexane	15.29	92.09	96.50	94.10	94.94	85.67	95.47
25	2-methoxy ethanol	15.48	95.40	95.21	88.76	89.58	105.69	84.88
26	2-methyl-1-propanol	15.48	103.70	100.67	93.50	90.64	104.39	89.10
27	1,2-Dimethoxy ethane	15.89	107.56	113.22	91.89	115.65	104.27	90.30
28	Benzene	16.01	96.25	91.79	98.40	87.77	92.33	90.31
29	Isopropyl acetate	16.23	96.01	90.69	94.33	82.99	95.72	88.83
30	2-methylTHF	16.53	99.19	85.63	82.04	83.68	95.94	89.03
31	Isooctane	16.65	99.95	105.51	102.20	80.99	92.41	98.40
32	Triethylamine	16.79	95.6	82.99	109.62	92.77	86.79	96.96
33	Heptane	17.29	112.23	96.41	108.04	115.52	88.02	96.02
34	1-Butanol	17.68	116.23	96.58	105.72	87.33	101.69	87.90
35	Trichloroethylene	18.18	99.99	97.41	99.05	87.05	86.82	96.71
36	Methylcyclohexane	18.99	100.57	82.26	119.14	90.28	87.1	96.46
37	1,4-Dioxane	19.06	105.05	95.38	100.3	80.92	89.24	92.38
38	n-Propyl acetate	19.29	109.75	89.06	82.11	80.62	95.69	89.61
39	2-ethoxyethanol	19.99	96.45	105.42	100.97	82.82	97.69	86.49
40	Methylisobutylketone	21.20	104.74	93.80	104.95	83.63	99.66	113.95
41	Pyridine	21.20	103.41	83.08	99.35	85.46	98.66	94.07
42	Cyclopentylmethylether	21.37	99.21	86.98	115.09	82.01	100.69	89.45
43	3-methyl-1-butanol	21.40	100.55	92.95	110.35	86.74	100.53	89.10
44	Toluene	21.77	107.60	92.85	101.71	81.06	90.43	92.59
45	Isobutyl acetate	22.12	97.85	90.12	114.10	82.81	98.42	89.34
46	1-Pentanol	22.70	100.24	103.98	97.73	98.74	99.06	100.99
47	2-Hexanone	23.36	108.26	99.27	102.29	83.05	99.41	90.08
48	Ethylene glycol	23.59	84.54	94.14	103.87	88.46	99.79	87.19
49	n-butyl acetate	23.81	100.45	90.94	111.74	83.67	98.25	89.24
50	n-DMF	24.28	107.48	99.49	90.31	85.54	96.47	89.84
51	Formamide	24.47	104.93	103.30	86.02	88.59	95.07	87.41
52	chlorobenzene	25.58	91.51	98.24	94.99	80.87	85.03	95.75
53	p-Xylene	26.44	101.63	97.33	98.89	80.69	87.79	93.49
54	DMSO	27.41	95.25	100.46	94.61	84.43	92.97	93.29
55	DMA	27.81	98.22	100.37	95.78	84.94	91.22	93.73
56	cumene	28.11	97.17	98.64	102.77	82.17	86.86	95.55
57	Anisole	28.19	97.12	97.48	90.11	83.40	87.43	93.25

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1 Table S10: Recovery results for Amitriptyline Hydrochloride (API) and Amitone 25 tablet.
2

Sr. No	Peak Name	RT (min)	Amitriptyline-Recovery			Amitone 25-Recovery		
			70%	110%	150%	70%	110%	150%
1	Methanol	5.26	112.41	90.71	100.69	82.78	85.69	111.17
2	Ethanol	6.67	115.77	89.80	116.67	83.21	83.98	103.94
3	Pentane	6.89	97.38	100.16	94.23	95.74	89.83	87.63
4	Ethyl ether	7.29	87.30	95.29	103.98	84.42	98.16	109.18
5	Acetone	7.67	103.94	102.79	103.42	96.47	82.43	85.87
6	1,1-Dichloroethene	7.98	109.05	87.67	92.58	88.71	86.61	98.09
7	Isopropyl alcohol	7.98	109.07	87.94	92.82	88.78	86.79	99.49
8	Ethyl formate	8.20	107.98	84.63	92.65	93.93	82.34	92.01
9	Acetonitrile	8.24	112.80	86.94	107.42	85.31	81.55	93.76
10	Methyl acetate	8.68	103.57	83.31	99.64	98.15	92.89	96.68
11	Dichloromethane	9.03	108.41	89.23	92.58	96.00	81.23	101.67
12	t-Butanol	9.14	107.38	86.48	88.93	85.93	85.76	97.87
13	MTBE	10.06	97.69	85.43	117.50	102.17	86.41	110.36
14	1-propanol	11.16	105.24	84.68	102.25	84.91	82.91	97.57
15	Hexane	11.17	109.48	89.69	89.39	100.10	85.44	101.10
16	Isopropyl ether	11.72	100.38	83.84	83.08	98.52	84.65	97.30
17	Nitromethane	12.48	109.95	89.03	85.09	100.96	87.41	111.45
18	Methyl ethyl ketone	12.93	107.30	85.80	100.15	85.80	87.37	97.95
19	Ethyl acetate	13.33	107.46	85.49	114.14	83.77	82.70	96.29
20	2-Butanol	13.57	107.48	86.51	89.70	86.00	85.67	87.99
21	THF	14.05	102.94	82.26	103.61	91.66	86.48	93.59
22	Trichloro methane	14.15	109.17	88.38	89.88	84.68	84.39	99.16
23	2,2-Dimethoxy propane	15.14	105.78	85.20	82.07	84.90	81.63	100.15
24	cyclohexane	15.29	95.49	105.71	105.74	94.94	84.27	108.42
25	2-methoxy ethanol	15.48	106.57	85.28	86.02	89.58	85.62	107.87
26	2-methyl-1-propanol	15.48	111.48	91.94	99.64	90.64	85.62	107.63
27	1,2-Dimethoxy ethane	15.89	104.02	102.33	91.20	115.65	103.45	100.93
28	Benzene	16.01	109.66	87.31	87.13	87.77	82.23	95.27
29	Isopropyl acetate	16.23	105.91	84.05	101.48	82.99	82.80	93.39
30	2-methylTHF	16.53	102.06	80.94	103.24	83.68	81.76	100.09
31	Isooctane	16.65	95.04	91.08	113.22	80.99	88.87	100.53
32	Triethylamine	16.79	101.51	80.74	106.15	92.77	87.50	108.79
33	Heptane	17.29	87.27	110.75	113.13	115.52	83.79	102.37
34	1-Butanol	17.68	110.02	87.13	114.73	87.33	85.86	90.78
35	Trichloroethylene	18.18	111.44	92.65	82.11	87.05	81.48	81.69
36	Methylcyclohexane	18.99	99.05	82.09	81.87	90.28	112.29	104.06
37	1,4-Dioxane	19.06	109.55	90.33	96.97	80.92	82.43	94.53
38	n-Propyl acetate	19.29	104.04	81.95	116.88	80.62	81.22	87.49
39	2-ethoxyethanol	19.99	115.26	97.02	103.49	82.82	83.33	94.35
40	Methylisobutylketone	21.20	105.14	82.99	102.48	83.63	82.40	101.05
41	Pyridine	21.20	104.47	114.85	97.15	85.46	96.45	101.33
42	Cyclopentylmethylether	21.37	101.90	107.44	115.32	82.01	83.57	83.35
43	3-methyl1-butanol	21.40	104.76	83.21	105.70	86.74	84.77	99.81
44	Toluene	21.77	107.41	86.81	100.09	81.06	82.43	99.29
45	Isobutyl acetate	22.12	102.91	81.60	111.40	82.81	82.93	88.19
46	1-Pentanol	22.70	119.39	92.77	97.28	98.74	94.52	110.89
47	2-Hexanone	23.36	110.53	94.38	88.47	83.05	91.21	102.76
48	Ethylene glycol	23.59	92.84	98.09	113.69	88.46	95.37	106.20
49	n-butyl acetate	23.81	104.03	81.63	114.44	83.67	83.16	88.49
50	n-DMF	24.28	114.32	90.75	82.45	85.54	84.55	104.17
51	Formamide	24.47	105.45	111.53	116.61	88.59	86.89	105.88
52	chlorobenzene	25.58	110.67	92.49	84.50	80.87	89.74	85.63
53	p-Xylene	26.44	110.98	91.24	98.13	80.69	94.63	80.77
54	DMSO	27.41	112.99	92.49	111.66	84.43	83.76	80.18
55	DMA	27.81	114.42	93.12	111.56	84.94	83.87	80.51
56	cumene	28.11	110.83	92.16	82.51	82.17	81.81	83.94
57	Anisole	28.19	110.89	90.45	103.42	83.40	95.24	81.83

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1 Table S11: Robustness was evaluated for split ratio and oven temperature variations using a Fenoterol Hydrobromide solution
 2 spiked with the 57-solvent mixture (100% level) and analyzed by MS-SIM.
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Sr. No	Peak Name	RT (min)	Split Ratio, % Recovery			Oven Temperature, % Recovery		
			35:1 (Standard)	33.5:1 (- 5%)	36.5:1 (+ 5%)	40°C (Standard)	38°C (- 5%)	42°C (+ 5%)
1	Methanol	5.25	106.06	97.53	99.86	106.06	101.43	102.09
2	Ethanol	6.68	104.20	96.19	100.18	104.20	100.51	101.46
3	Pentane	6.91	102.09	95.51	101.61	102.09	95.76	98.58
4	Ethyl ether	7.31	104.57	95.08	100.94	104.57	98.84	100.72
5	Acetone	7.71	103.52	95.02	101.18	103.52	99.82	100.65
6	1,1-Dichloroethene	7.71	107.52	98.79	98.52	107.52	101.90	103.75
7	Isopropyl alcohol	8.02	102.41	95.32	100.94	102.41	98.97	100.69
8	Ethyl formate	8.24	102.89	95.49	101.10	102.89	98.86	100.74
9	Acetonitrile	8.25	101.75	93.89	102.72	101.75	99.58	95.32
10	Methyl acetate	8.71	104.07	92.90	100.03	104.07	100.21	100.93
11	Dichloromethane	9.08	105.53	95.62	98.50	105.53	102.41	102.94
12	t-Butanol	9.18	101.38	91.18	101.11	101.38	98.83	100.65
13	Methyl tert-butyl ether	10.11	102.63	93.94	100.54	102.63	99.50	101.55
14	Hexane	11.23	101.22	94.06	101.43	101.22	98.41	101.49
15	1-Propanol	11.23	101.78	94.61	100.79	101.78	99.63	99.94
16	Iso propyl ether	11.78	105.93	97.48	99.48	105.93	101.39	103.42
17	Nitromethane	12.45	105.45	98.57	96.75	105.45	105.21	96.81
18	Methyl ethyl ketone	13.01	103.33	96.90	100.23	103.33	100.23	101.49
19	Ethyl acetate	13.39	103.76	95.53	99.81	103.76	100.36	101.98
20	2-Butanol	13.65	106.48	84.30	96.36	106.48	95.30	100.65
21	Tetrahydrofuran	14.12	104.02	93.82	100.07	104.02	100.52	101.55
22	Trichloromethane	14.24	103.90	95.27	99.69	103.90	100.79	100.86
23	2,2-Dimethoxy propane	15.2	103.63	97.78	89.09	103.63	102.48	97.24
24	Cyclohexane	15.37	107.93	101.36	94.43	107.93	99.40	99.51
25	2-Methyl-1-propanol	15.37	104.66	96.93	99.68	104.66	100.03	100.10
26	2-Methoxy ethanol	15.58	107.16	87.82	98.43	107.16	99.00	101.07
27	1,2-Dimethoxy ethane	16.09	105.07	92.02	100.60	105.07	96.70	94.46
28	Benzene	16.09	105.42	96.25	99.49	105.42	101.96	90.69
29	Isopropyl acetate	16.31	105.99	95.00	100.38	105.99	100.55	109.36
30	2-Methyl tetrahydrofuran	16.59	105.24	94.14	100.35	105.24	100.07	100.20
31	Iso octane	16.73	103.20	95.25	100.38	103.20	98.44	99.65
32	Triethylamine	16.78	104.56	99.14	99.50	104.56	100.35	102.55
33	Heptane	17.36	104.08	99.58	100.81	104.08	99.05	99.92
34	1-Butanol	17.76	95.30	99.39	100.49	95.30	99.61	85.06
35	Trichloroethylene	18.25	105.33	102.57	98.58	105.33	102.10	96.90
36	Methylcyclohexane	19.07	107.02	100.25	100.54	107.02	100.13	103.11
37	1,4-Dioxane	19.11	105.17	100.44	99.22	105.17	101.64	98.00
38	n-Propyl acetate	19.36	105.97	99.54	100.94	105.97	100.31	84.20
39	2-Ethoxyethanol	19.98	106.49	101.68	98.13	106.49	101.35	102.18
40	Pyridine	21.26	104.71	98.05	98.51	104.71	100.50	100.95
41	Methylisobutylketone	21.27	90.27	96.57	101.88	90.27	95.33	100.36
42	Cyclopentyl methyl ether	21.27	103.83	95.31	97.39	103.83	97.96	97.86
43	3-Methyl-1-butanol	21.46	103.80	98.84	100.22	103.80	100.11	95.80
44	Toluene	21.83	112.55	97.36	94.57	112.55	101.07	94.14
45	Iso butyl acetate	22.18	102.06	99.74	101.23	102.06	102.88	100.92
46	1-Pentanol	22.75	93.04	96.77	87.22	93.04	99.41	94.09
47	2-Hexanone	23.4	97.62	99.78	101.12	97.62	99.17	100.96
48	Ethylene glycol	23.58	108.27	97.23	101.97	108.27	103.71	100.54
49	n-Butyl acetate	23.86	97.01	99.67	101.85	97.01	99.88	103.88
50	Formamide	23.99	106.80	98.78	106.35	106.80	98.72	95.80
51	Dimethylformamide	24.28	92.75	89.79	103.79	92.75	99.48	97.97
52	Chlorobenzene	25.65	109.65	101.35	98.79	109.65	102.03	101.37
53	p-Xylene	26.52	106.10	101.46	98.74	106.10	101.90	101.30
54	Dimethyl sulfoxide	27.41	104.52	101.20	99.94	104.52	101.74	102.99
55	Dimethylacetamide	27.83	104.44	98.78	99.64	104.44	110.93	100.14
56	Cumene	28.17	99.00	100.50	100.19	99.00	108.72	103.10
57	Anisole	28.26	104.45	101.92	97.93	104.45	106.99	104.72

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Table S12: Robustness was evaluated for flow-rate variations using a Fenoterol Hydrobromide solution spiked with the 57-solvent mixture (100% level) and analyzed by MS-SIM.

Sr. No	Peak Name	RT (min)	Carrier Gas flow rate (mL/min), % Recovery		
			5 mL/min (Standard)	4.75 mL/min (- 5%)	5.25 mL/min (+ 5%)
1	Methanol	5.25	106.06	100.99	94.09
2	Ethanol	6.68	104.20	100.71	98.36
3	Pentane	6.91	102.09	96.66	97.64
4	Ethyl ether	7.31	104.57	99.03	100.52
5	Acetone	7.71	103.52	99.77	102.10
6	1,1-Dichloroethene	7.71	107.52	102.18	98.85
7	Isopropyl alcohol	8.02	102.41	99.73	101.99
8	Ethyl formate	8.24	102.89	99.67	99.35
9	Acetonitrile	8.25	101.75	100.40	96.04
10	Methyl acetate	8.71	104.07	100.70	99.92
11	Dichloromethane	9.08	105.53	102.01	101.81
12	t-Butanol	9.18	101.38	100.29	100.67
13	Methyl tert-butyl ether	10.11	102.63	99.88	101.26
14	Hexane	11.23	101.22	99.65	100.90
15	1-Propanol	11.23	101.78	102.11	99.13
16	Iso propyl ether	11.78	105.93	102.03	99.32
17	Nitromethane	12.45	105.45	96.27	105.20
18	Methyl ethyl ketone	13.01	103.33	101.60	99.24
19	Ethyl acetate	13.39	103.76	101.81	101.22
20	2-Butanol	13.65	106.48	101.62	97.31
21	Tetrahydrofuran	14.12	104.02	101.54	98.36
22	Trichloromethane	14.24	103.90	102.92	98.36
23	2,2-Dimethoxy propane	15.20	103.63	103.06	100.44
24	Cyclohexane	15.37	107.93	100.70	100.56
25	2-Methyl 1-propanol	15.37	104.66	100.97	99.40
26	2-Methoxy ethanol	15.58	107.16	102.17	101.06
27	1,2-Dimethoxy ethane	16.09	105.07	106.71	108.66
28	Benzene	16.09	105.42	102.23	104.67
29	Isopropyl acetate	16.31	105.99	101.58	99.79
30	2-Methyl tetrahydrofuran	16.59	105.24	101.78	101.01
31	Iso octane	16.73	103.20	100.50	99.72
32	Triethylamine	16.78	104.56	101.98	106.81
33	Heptane	17.36	104.08	100.02	100.32
34	1-Butanol	17.76	95.30	101.78	101.45
35	Trichloroethylene	18.25	105.33	102.77	100.62
36	Methylcyclohexane	19.07	107.02	100.97	100.93
37	1,4-Dioxane	19.11	105.17	102.87	92.32
38	n-Propylacetate	19.36	105.97	101.57	98.91
39	2-Ethoxyethanol	19.98	106.49	105.78	112.88
40	Pyridine	21.26	104.71	100.34	89.55
41	Methylisobutylketone	21.27	90.27	100.75	101.64
42	Cyclopentyl methyl ether	21.27	103.83	111.20	94.15
43	3-Methyl 1-butanol	21.46	103.80	94.16	100.33
44	Toluene	21.83	112.55	102.01	99.76
45	Iso butyl acetate	22.18	102.06	100.12	98.74
46	1-Pentanol	22.75	93.04	100.65	99.90
47	2-Hexanone	23.40	97.62	100.39	96.51
48	Ethylene glycol	23.58	108.27	101.92	99.24
49	n-Butyl acetate	23.86	97.01	100.40	100.93
50	Formamide	23.99	106.80	104.38	98.00
51	Dimethylformamide	24.28	92.75	101.95	103.07
52	Chlorobenzene	25.65	109.65	102.89	101.30
53	p-Xylene	26.52	106.10	102.69	99.54
54	Dimethyl sulfoxide	27.41	104.52	102.28	101.15
55	Dimethylacetamide	27.83	104.44	102.75	102.50
56	Cumene	28.17	99.00	103.18	100.36
57	Anisole	28.26	104.45	102.23	99.50

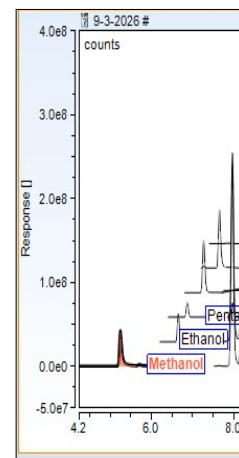
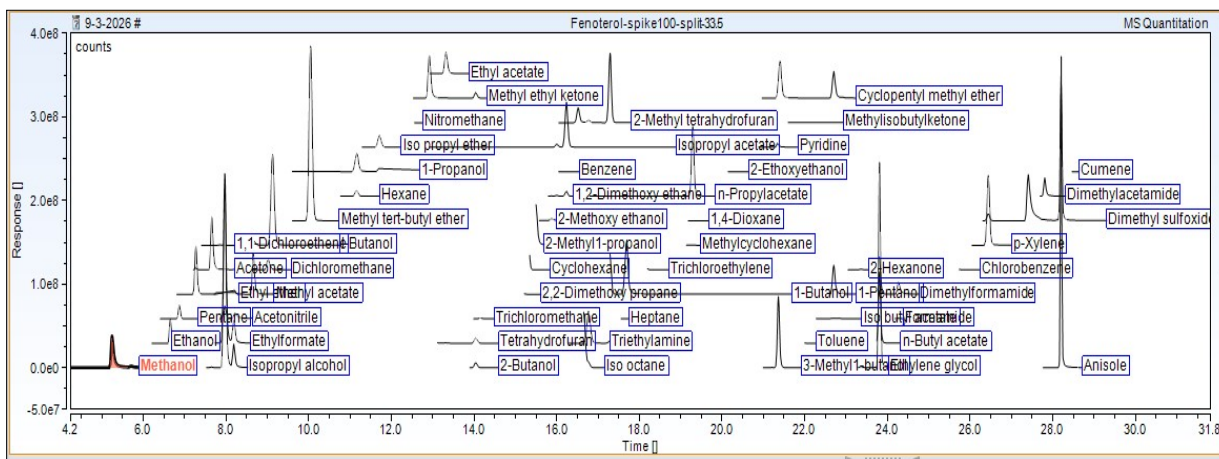


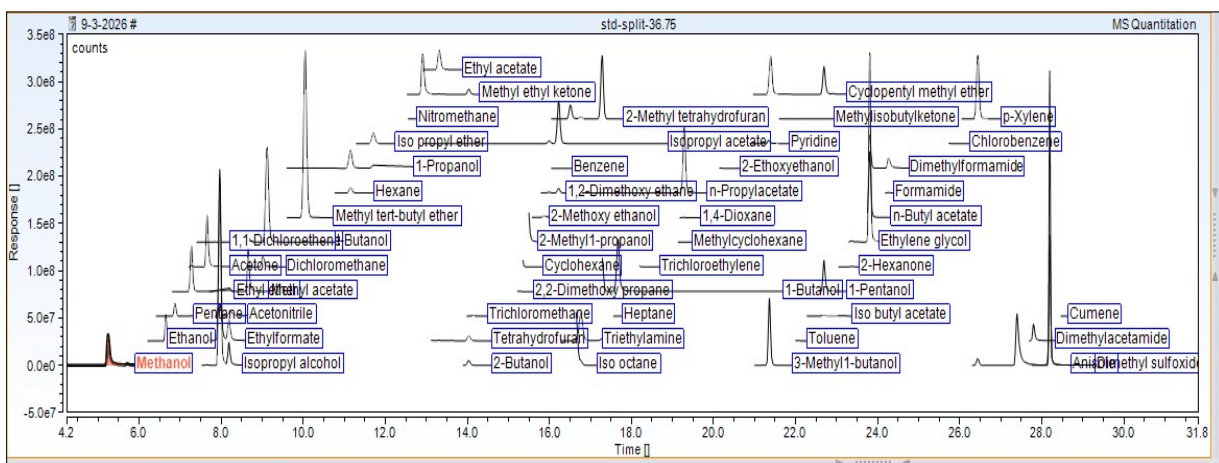
Figure S16: Robustness was evaluated at a split ratio of 33.5 using the optimized method; a standard solution of 57-solvent mixture (100% level) without Fenoterol Hydrobromide was analyzed by MS-SIM.



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2 Figure S17: Robustness was evaluated at a split ratio of 33.5 using the optimized method; a Fenoterol Hydrobromide solution spiked
3 with the 57-solvent mix (100% level) was analyzed by MS-SIM.

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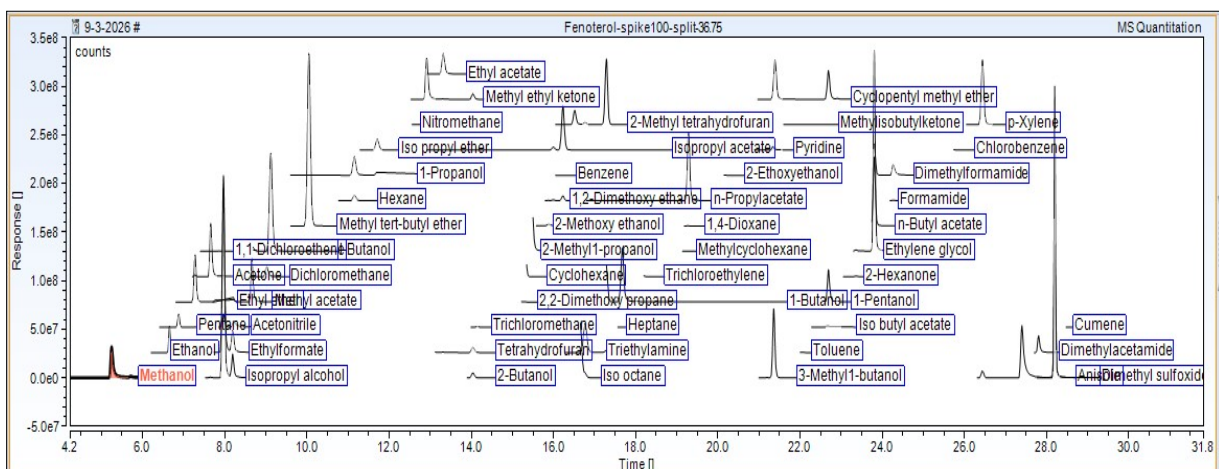


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6 Figure S18: Robustness was evaluated at a split ratio of 36.75 using the optimized method; a standard solution of 57-solvent mix (100%
7 level) without Fenoterol Hydrobromide was analyzed by MS-SIM.

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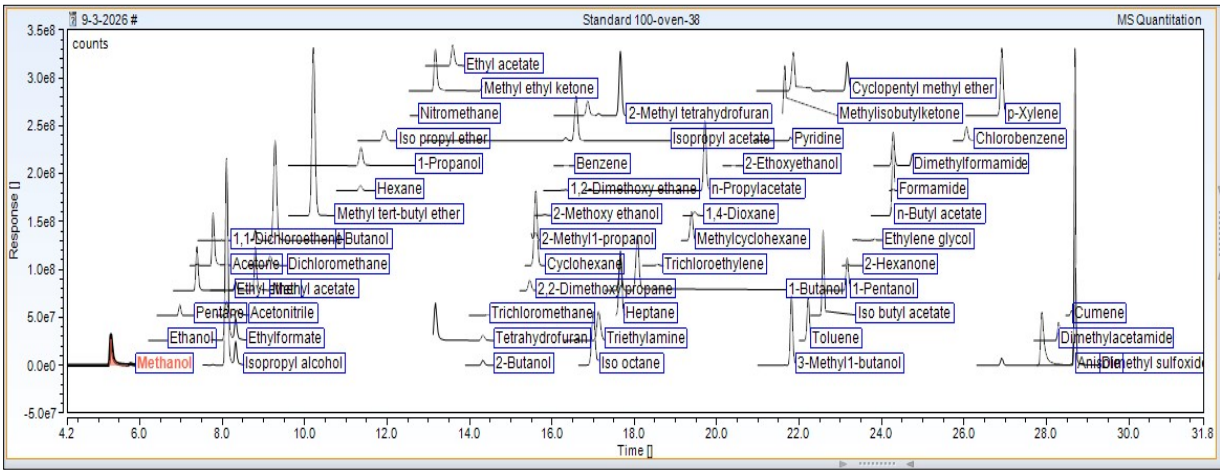
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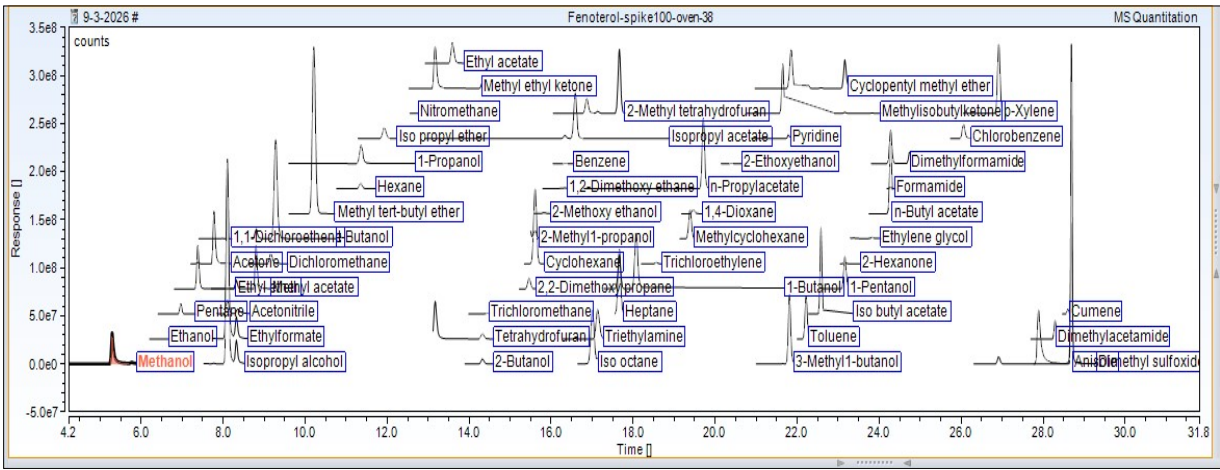
11 Figure S19: Robustness was evaluated at a split ratio of 36.75 using the optimized method; a Fenoterol Hydrobromide solution spiked
12 with the 57-solvent mix (100% level) was analyzed by MS-SIM.

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 2 Figure S20: Robustness was evaluated at an oven temperature 38°C using the optimized method; a standard solution of 57-solvent mix
 3 (100% level) without Fenoterol Hydrobromide was analyzed by MS-SIM.

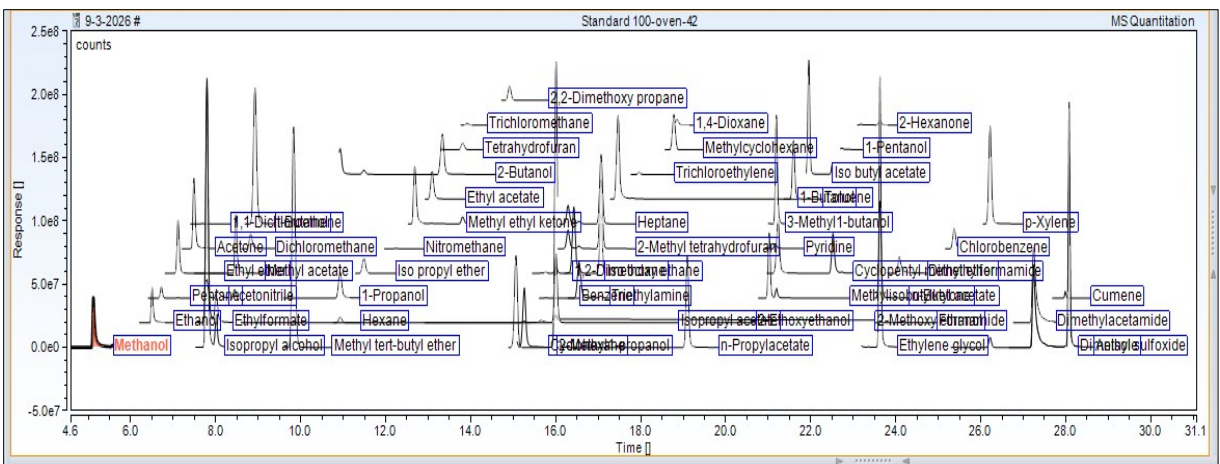
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 6 Figure S21: Robustness was evaluated at an oven temperature 38°C using the optimized method; a Fenoterol Hydrobromide solution
 7 spiked with the 57-solvent mix (100% level) was analyzed by MS-SIM.

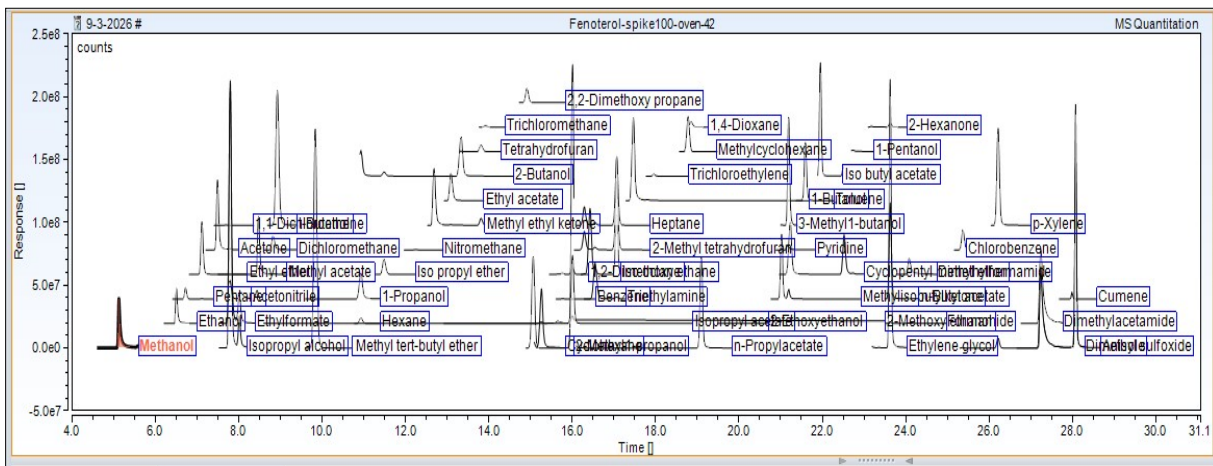
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 11 Figure S22: Robustness was evaluated at an oven temperature 42°C using the optimized method; a standard solution of 57-solvent mix
 12 (100% level) without Fenoterol Hydrobromide was analyzed by MS-SIM.

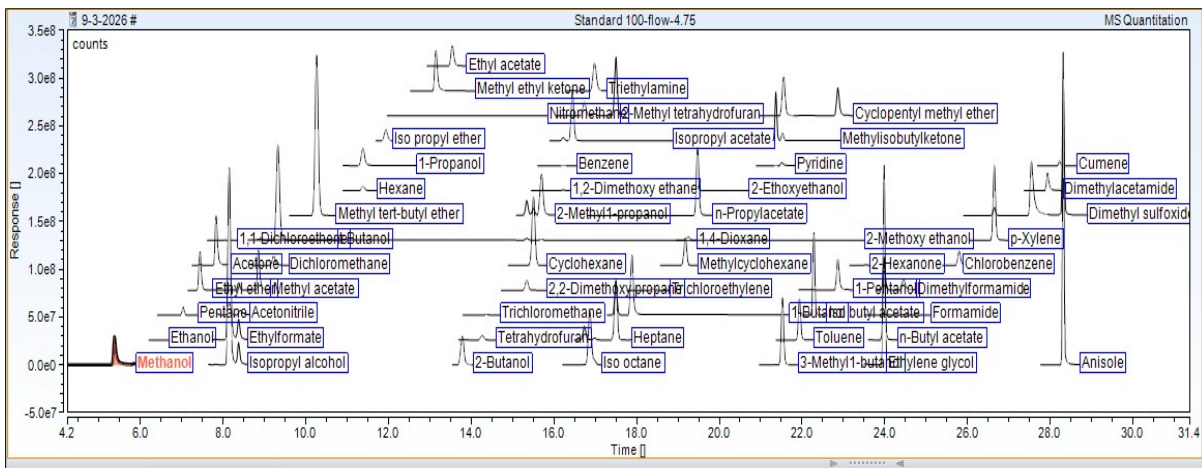
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2 Figure S23: Robustness was evaluated at an oven temperature 42°C using the optimized method; a Fenoterol Hydrobromide solution
 3 spiked with the 57-solvent mix (100% level) was analyzed by MS-SIM.

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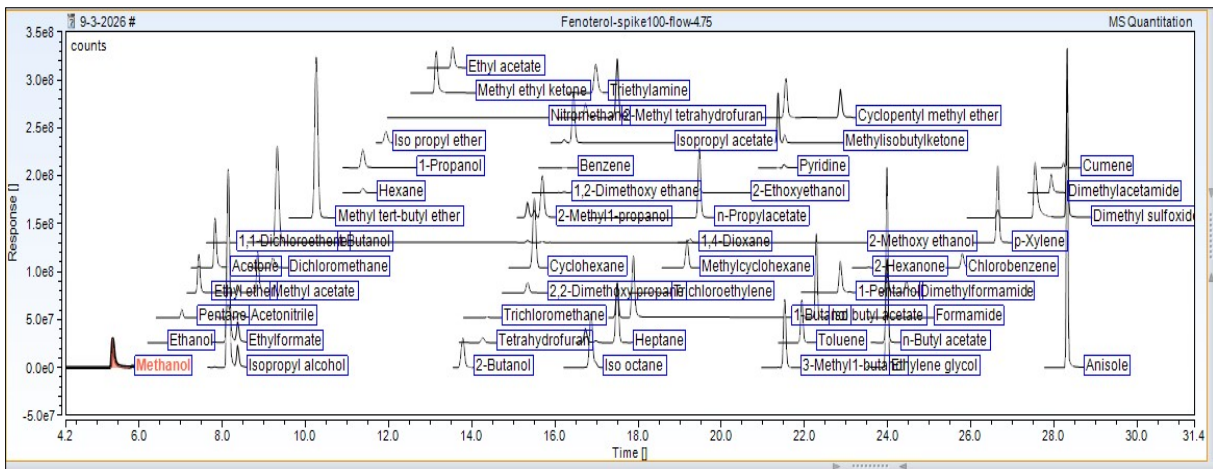


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6 Figure S24: Robustness was evaluated at a flow rate 4.75 ml/min using the optimized method; a standard solution of 57-solvent mix
 7 (100% level) without Fenoterol Hydrobromide was analyzed by MS-SIM.

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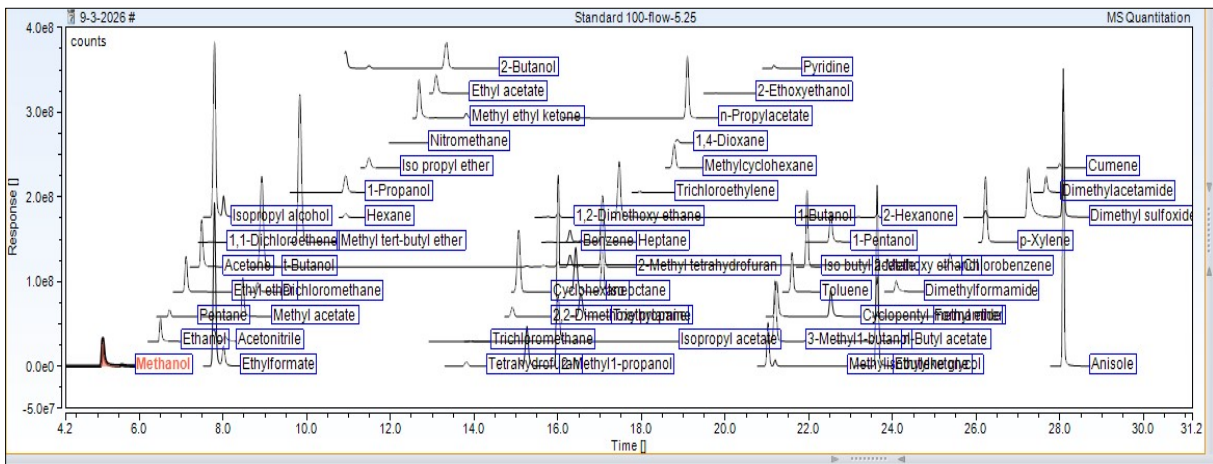
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11 Figure S25: Robustness was evaluated at a flow rate 4.75 ml/min using the optimized method; a Fenoterol Hydrobromide solution spiked
 12 with the 57-solvent mix (100% level) was analyzed by MS-SIM.

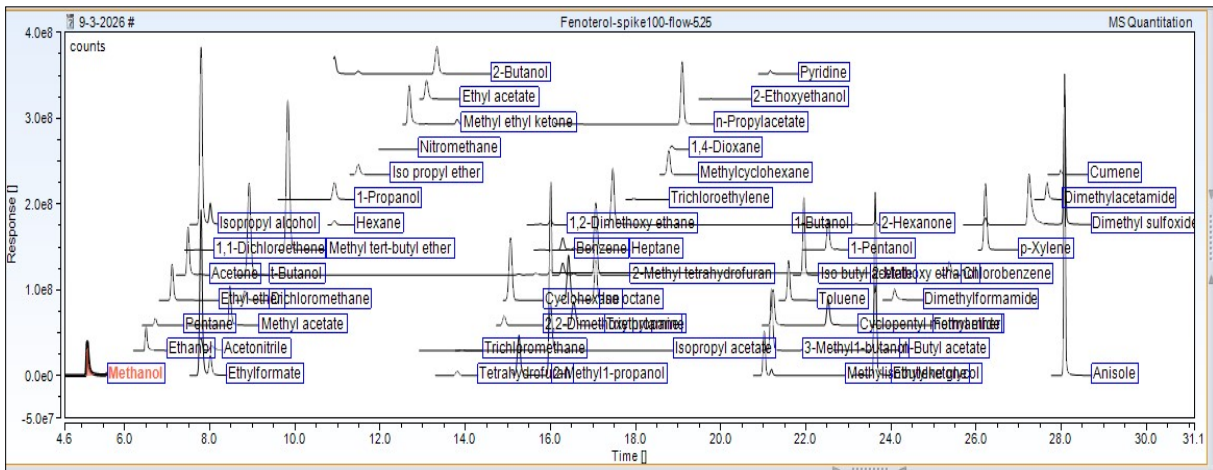
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2 Figure S26: Robustness was evaluated at a flow rate 5.25 ml/min using the optimized method; a standard solution of 57-solvent mix
 3 (100% level) without Fenoterol Hydrobromide was analyzed by MS-SIM.

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6 Figure S27: Robustness was evaluated at a flow rate 5.25 ml/min using the optimized method; a Fenoterol Hydrobromide solution spiked
 7 with the 57-solvent mix (100% level) was analyzed by MS-SIM.