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Residual Solvents by HT3™ Headspace in Reference to USP 467 with a Comparison of Static Versus Dynamic Headspace Analysis

Application Note

By: James Cox

Introduction

Residual solvents in pharmaceuticals are defined as volatile organic chemicals that are used or produced in the manufacture of drug substances, excipients or in the preparation of drug products. Because residual solvents do not provide therapeutic benefits, they should be removed, to the extent possible. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Looking forward to the implementation of a revised USP 467 method, Teledyne Tekmar evaluated the new protocol, therefore this application will comply with the procedure and criteria changes set forth in the USP30 NF25, Second Supplement (effective December 1, 2007) and the interim revision announcement. (1)

Figure 1: HT3 Headspace Autosampler

Instrument Parameters:

The HT3 Headspace Analyzer was connected to an Agilent 5973/6890 GC/FID system. Instrument conditions for the HT3 (loop and trap), GC and FID are presented in Tables 1,2 and 3 respectively.

Variable	Value
Constant Heat Time	On
GC Cycle Time	70 min
Valve Oven Temp	120°C
Transfer Line Temp	120°C
Standby Flow Rate	10mL/min
Platen/Sample Temp	40°C
Platen Temp Equil. Time	0.20 min
Sample Equil. Time	45.00 min
Mixer	Off
Mixing Time	0.0 min

Variable (Cont'd)	Value
Mixing Level	Level 5
Mixer Stabilize Time	0.50 min
Pressurize	10 psig
Pressurize Time	2.0 min
Pressure Equil. Time	0.50 min
Loop Fill Pressure	5 psig
Loop Fill Time	2.00 min
Loop Fill Equil. Time	0.50 min
Inject Time	1.00 min

Table 1. HT3 Parameters (Loop)

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4736 Socialville Foster Rd., Mason, OH 45040
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Variable	Value
Valve Oven Temp	120°C
Transfer Line Temp	120°C
Standby Flow Rate	50 mL/min
Trap Standby Temp.	30 °C
Trap Sweep Temp.	0 °C
Platen/Sample Temp	40°C
Platen Temp.Equil.Time	1.00 min
Sample Preheat Time	45.00 min
Preheat Mixer	Off
Preheat Mixer Level	5
Preheat Mixing Time	0.00 min
Preheat Mixer Stabilize Time	2.00 Min.

Variable	Value
Sweep Flow Rate	75mL/min
Sweep Flow Time	11.00 min.
Dry Purge Time	2.00 min
Dry Purge Time	2.00 min
Dry Purge Flow	200 mL/min
Dry Purge Temp.	25°C
Desorb Preheat	245°C
Desorb Temp.	250°C
Desorb Time	2.00 min
Trap Bake Temp.	260°C
Trap Bake Time.	10.00 min
Trap Bake Flow	400 mL/min.
Trap	K (Vocarb)

Table 2. HT3 Parameters (Trap)

Column	RTX-1301 (624) 30m x 0.32, 1.8 micrometer film, constant column flow of 2.16 mL/minutes
Inlet	Split ratio 5:1, total flow of 35.3 cm/sec, inlet temperature of 140°C
Oven	Initial temperature 40°C, hold for 20 minutes, rate of 10.0°C /min to 240 °C, hold for 20 minutes.
FID	250°C

Table 3. Agilent 6890 Conditions

Standard Preparation:

Stock concentrations were formulated at the following concentrations in DMSO:

Class 1, Loop--1000ug/mL Trap—1000ug/mL

Class 2 Subset A Loop--100,000ug/mL Trap—1000ug/mL

Class 2 Subset B-C Loop--10,000ug/mL Trap—1000ug/mL

From the stock concentrations working solutions were prepared in 10mL of DI water to create the working calibration. MDL data was calculated by running replicate samples at N=10 of a 10ppb solution. Calibration and MDL data are presented in Tables 4 and 5 respectively.

Compounds	r^2 Values	Curve range	MDL (ppm)	ICH Concentration Limit (ppm)	Class
Benzene	0.999	0.5ppm-10ppm	0.21	2	1
1,2-dichloroethane	0.999	1.25ppm-25ppm	0.44	5	1
1,1,1-trichloroethane	0.999	2.5ppm-50ppm	1.15	1500	1
1,1-Dichloroethylene	0.998	4ppm-40ppm	0.83	8	1
Carbon Tetrachloride	0.997	2ppm-100ppm	0.65	4	1
Methanol	0.999	300ppm-5000ppm	5.62	3000	2
Acetonitrile	0.999	300ppm-5000ppm	10.23	410	2
Tetrahydrofuran	0.999	300ppm-5000ppm	5.46	720	2
Hexane	0.999	50ppm-1000ppm	8.03	290	2
Nitromethane	1.000	50ppm-1000ppm	9.43	50	2
Chloroform	1.000	50ppm-1000ppm	8.09	60	2
1,2-dimethoxyethane	0.999	50ppm-1000ppm	6.29	100	2
Trichloroethane	1.000	50ppm-1000ppm	7.45	80	2
Pyridine	1.000	50ppm-1000ppm	8.86	200	2
2-Hexanone *	0.999	50ppm-1000ppm	6.85	Unlisted	2
1,2,3,4-tetrahydronaphthalene	1.000	50ppm-1000ppm	7.21	Unlisted	2
cis 1,2-dichloroethene *	0.998	100ppm-2000ppm	7.80	Unlisted	2
Cyclohexane	0.999	100ppm-2000ppm	6.37	3880	2
Dichloromethane	0.999	100ppm-2000ppm	9.01	600	2
2trans 1,2-dichloroethene *	1.000	100ppm-2000ppm	5.72	Unlisted	2
Methylcyclohexane	0.999	100ppm-2000ppm	8.17	1180	2
1,4-dioxane	1.000	100ppm-2000ppm	6.89	380	2
Toluene	1.000	100ppm-2000ppm	7.26	890	2
Chlorobenzene	1.000	100ppm-2000ppm	7.33	360	2
Ethylbenzene *	1.000	100ppm-2000ppm	7.71	Unlisted	2
M&P-xylene	0.999	200ppm-4000ppm	12.31	2170	2
O-xylene	1.000	100ppm-2000ppm	9.43	2170	2
N,N-dimethylformamide	1.000	50ppm-1000ppm	7.64	880	2
N,N-dimethylacetamide	1.000	50ppm-1000ppm	8.46	1090	2

Table 4. Residual Solvents Calibration Data (Loop)

*Compounds included in standard mix but not listed in USP <467> second supplement

Compounds	r^2 Values	Curve range	MDL (ppb)	ICH Concentration Limit (ppm)	Class
Benzene	0.999	5ppb-160ppb	1.32	2	1
1,2-dichloroethane	0.996	10ppb-320ppb	1.32	5	1
1,1,1-trichloroethane	0.997	10ppb-320ppb	1.41	1500	1
1,1-Dichloroethylene	0.999	5ppb-160ppb	1.18	8	1
Carbon Tetrachloride	0.998	5ppb-160ppb	1.54	4	1
Methanol	1.000	200ppb-10000ppb	70.0	3000	2
Acetonitrile	1.000	200ppb-10000ppb	90.0	410	2
Tetrahydrofuran	0.999	200ppb-10000ppb	100.0	720	2
Hexane	1.000	10ppb-800ppb	2.14	290	2
Nitromethane #					2
Chloroform	0.997	10ppb-800ppb	1.73	60	2
1,2-dimethoxyethane	1.000	10ppb-800ppb	2.67	100	2
Trichloroethane	1.000	10ppb-800ppb	2.21	80	2
Pyridine	1.000	10ppb-800ppb	4.07	200	2
2-Hexanone *	0.999	10ppb-800ppb	3.99	Unlisted	2
1,2,3,4-tetrahydronaphthalene	1.000	10ppb-800ppb	2.50	Unlisted	2
cis 1,2-dichloroethene *	0.998	10ppb-800ppb	2.19	Unlisted	2
Cyclohexane	1.000	10ppb-800ppb	1.89	3880	2
Dichloromethane	0.998	10ppb-800ppb	1.99	600	2
trans 1,2-dichloroethene *#					
Methylcyclohexane	1.000	10ppb-800ppb	2.34	1180	2
1,4-dioxane	1.000	10ppb-800ppb	2.51	380	2
Toluene	1.000	10ppb-800ppb	1.96	890	2
Chlorobenzene	0.997	10ppb-800ppb	2.04	360	2
Ethylbenzene *	1.000	10ppb-800ppb	2.11	Unlisted	2
M&P-xylene	0.999	20ppb-160.0ppb	2.34	2170	2
O-xylene	1.000	10ppb-800ppb	1.69	2170	2
N,N-dimethylformamide	1.000	10ppb-800ppb	3.07	880	2
N,N-dimethylacetamide	1.000	10ppb-800ppb	2.06	1090	2

Table 5. Residual Solvents Calibration Data (Trap)

*Compounds included in standard mix but not listed in USP <467> second supplement

Compounds not detected at low levels

Data:

Chromatography for all residual solvents investigated have excellent peak shape and response. Several stock standards where prepared containing full as well as subset target analytes at various concentrations so that the individual targets could be visibly seen without coelution. Chromatography for the standards

Investigated is presented below in Figures 1-5

Sample Chromatograms:

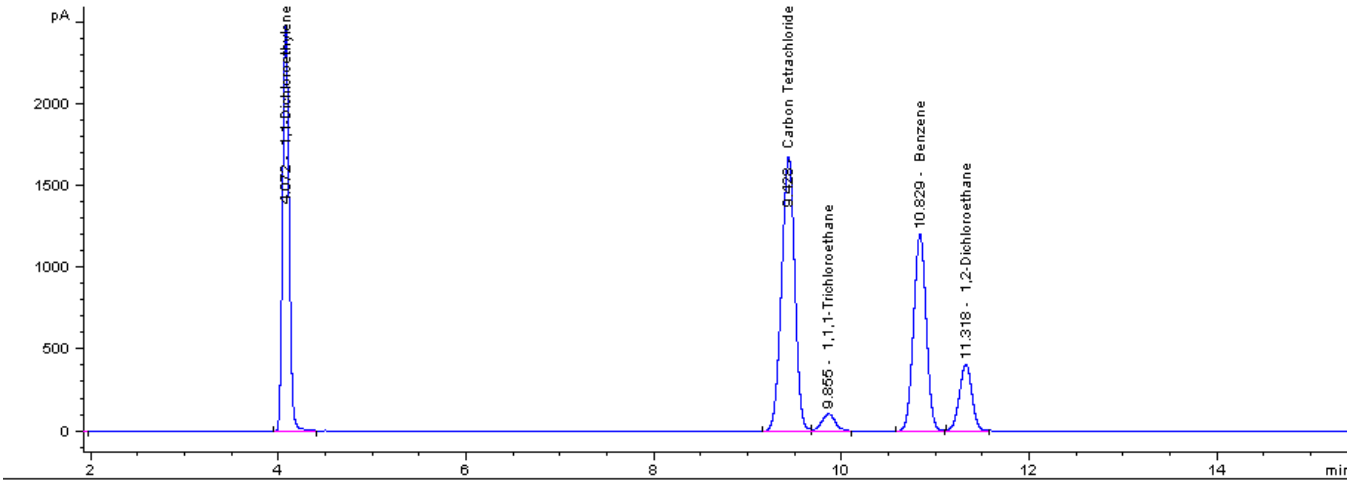

Figure 1. Class 1 Solvents @ 40ppm (Loop)

(1,1-Dichloroethylene, 1,1,1-Trichloroethane, Carbon Tetrachloride, Benzene and 1,2-Dichloroethane Respectively)

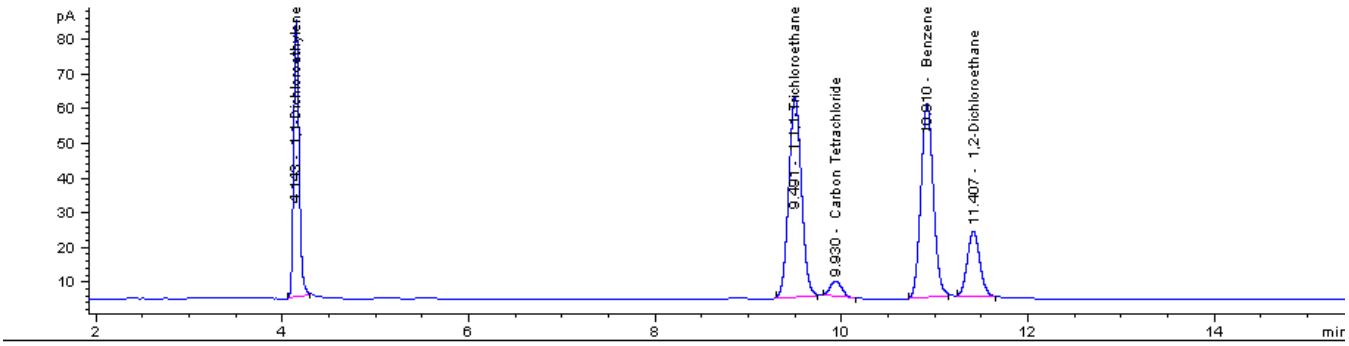

Figure 1a. Class 1 Solvents @ 10 & 20 ppb (Trap)

(1,1-Dichloroethylene, 1,1,1-Trichloroethane, Carbon Tetrachloride, Benzene and 1,2-Dichloroethane Respectively)

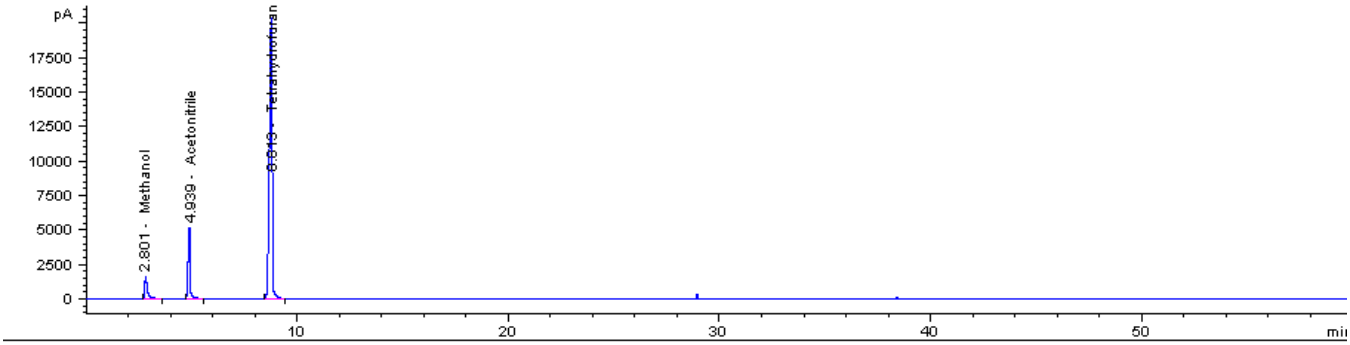

Figure 2. Class 2 Solvents @ 2500ppm (Loop)

(Methanol, Acetonitrile and Tetrahydrofuran respectively)

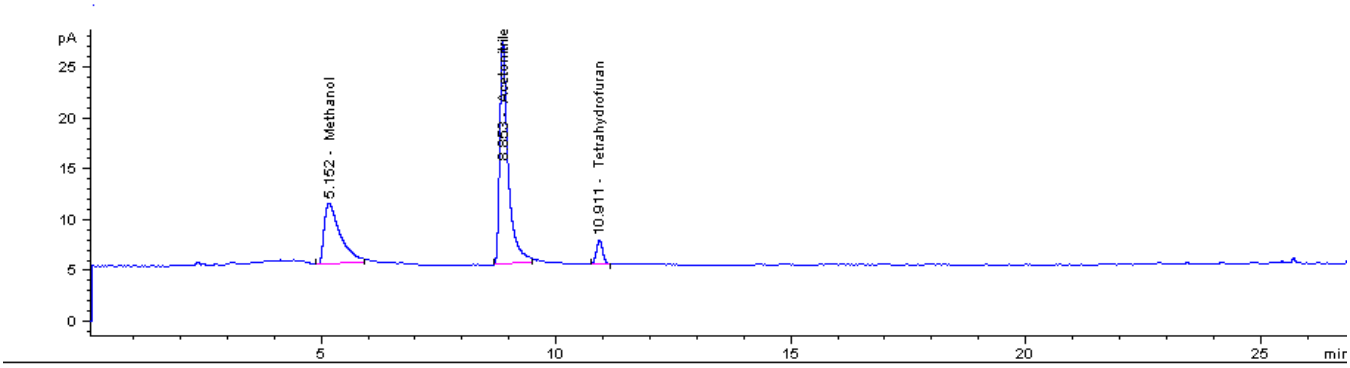

Figure 2a. Class 2 Solvents @ 0.5ppm (Trap)

(Methanol, Acetonitrile and Tetrahydrofuran respectively)

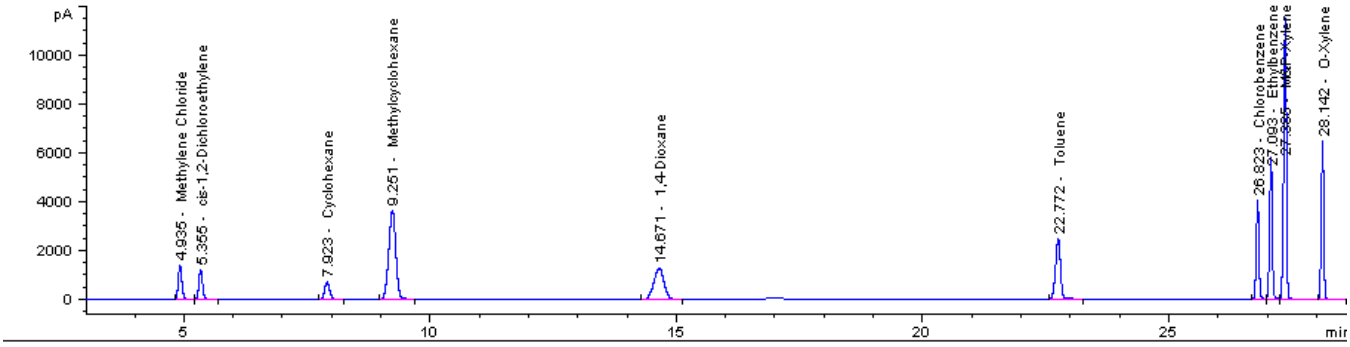

Figure 3. Class 2 Solvents @ 2500ppm (Loop)

Methylene Chloride, cis 1,2-Dichloroethylene, Cyclohexane, Methylcyclohexane, 1,4-Dioxane, Toluene, Chlorobenzene, Ethylbenzene, M&P-Xylene and O-Xylene Respectively)

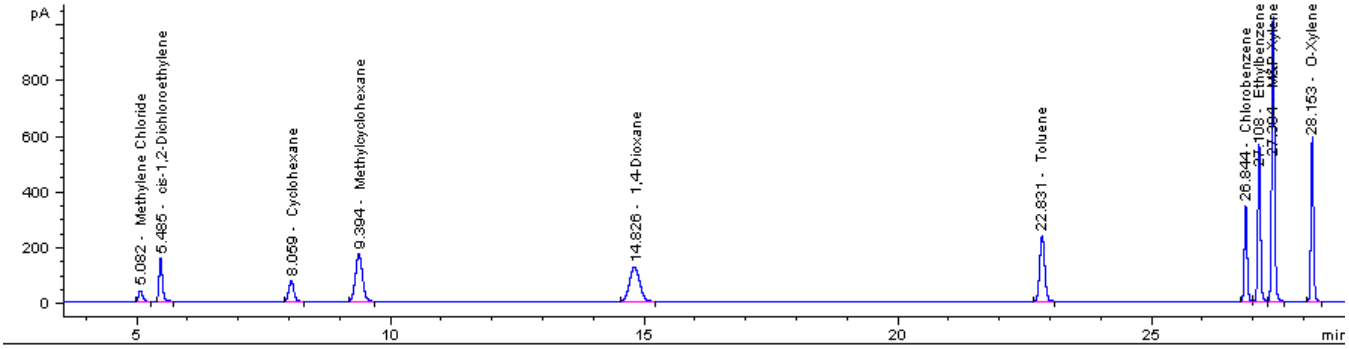

Figure 3a. Class 2 Solvents @ 10.0ppb (Trap)

Methylene Chloride, cis 1,2-Dichloroethylene, Cyclohexane, Methylcyclohexane, 1,4-Dioxane, Toluene, Chlorobenzene, Ethylbenzene, M&P-Xylene and O-Xylene Respectively)

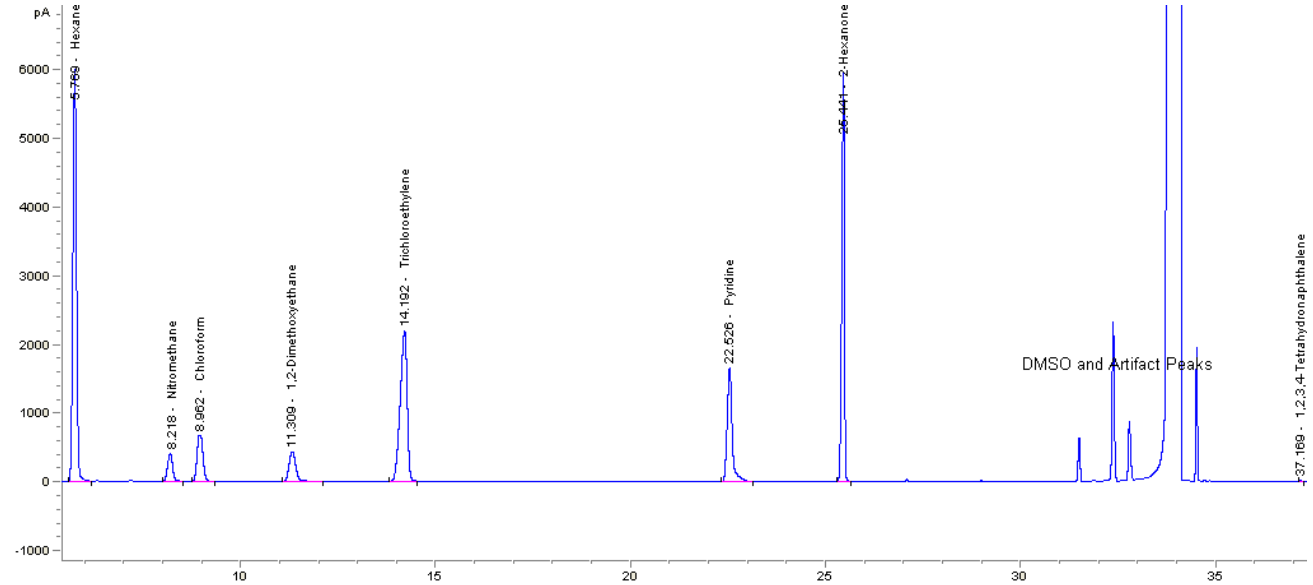

Figure 4. Class 2 Solvents @ 1000ppm (Loop)

(Hexane, Nitromethane, Chloroform, 1,2-Dimethoxyethane, Trichloroethylene, Pyridine, Hexanone, DMSO artifact peaks (next 7) and 1,2,3,4-Tetrahdronapthalene Respectively)

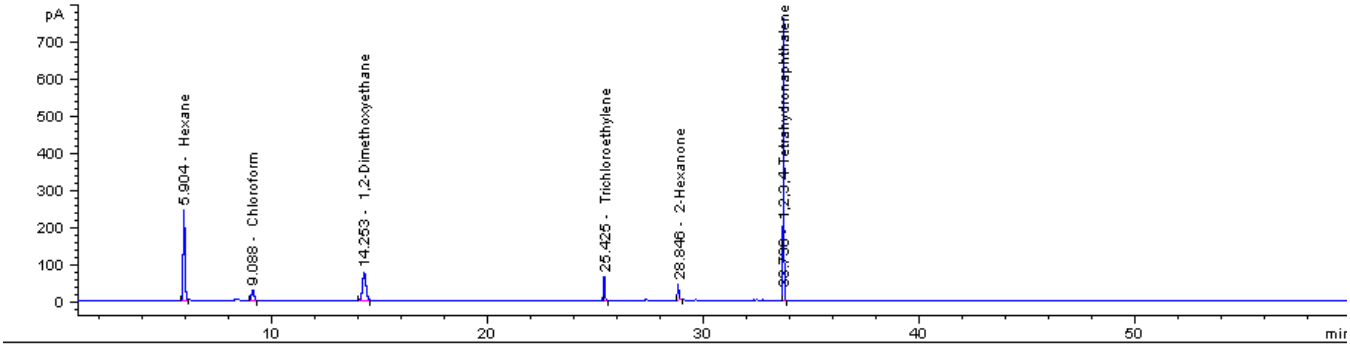

Figure 4a. Class 2 Solvents @ 10.0ppb (Trap)

(Hexane, Chloroform, 1,2-Dimethoxyethane, Trichloroethylene, Pyridine, Hexanone, and 1,2,3,4-Tetrahdronapthalene Respectively)

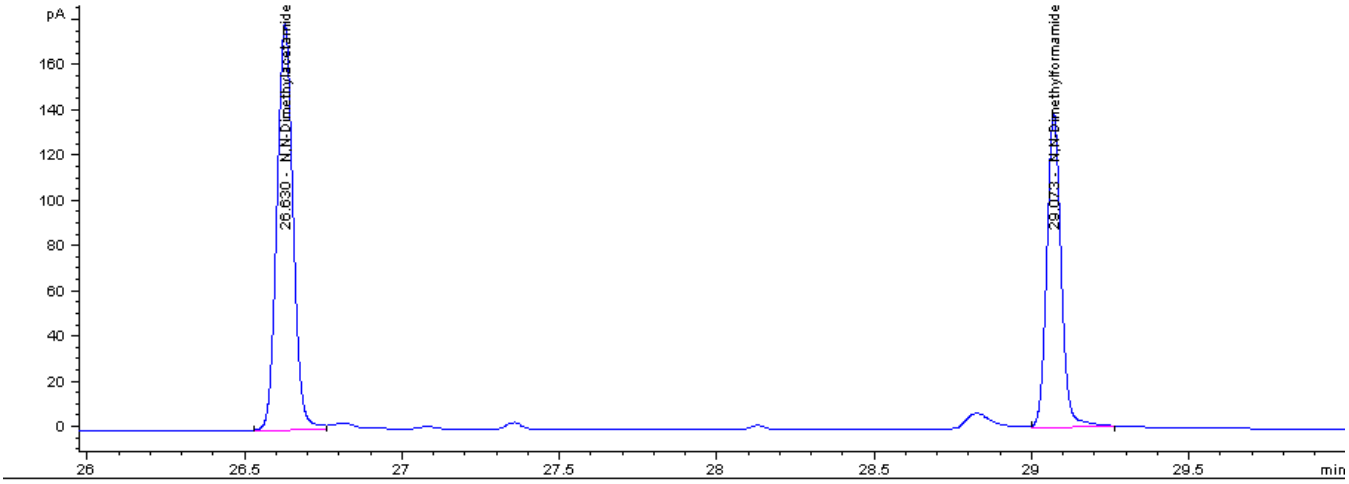

Figure 5. Class 2 Solvents @ 500ppm (Loop)

N,N-Dimethylformamide and N,N-Dimethylacetamide

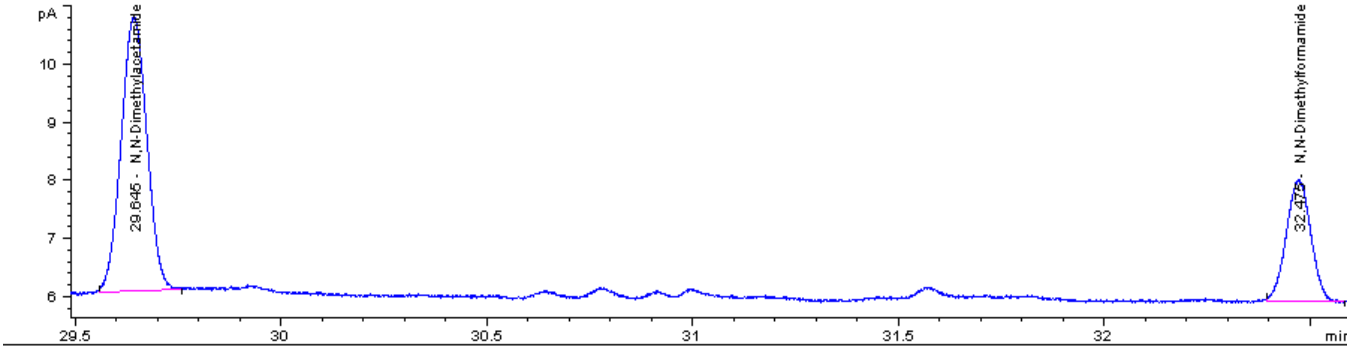

Figure 5a. Class 2 Solvents @ 10.0ppb (Trap)

N,N-Dimethylformamide and N,N-Dimethylacetamide

Conclusion:

Implementing USP30 NF25, Second Supplement with other revisions for USP <467> can be difficult. Teledyne Tekmar provides an application comparing both static and dynamic headspace that where MDL's greatly exceed USP Method requirements. Although static headspace is the validated USP methodology for residual solvent analysis, Teledyne Tekmar demonstrates that dynamic headspace can result in dramatically lower MDL's guaranteeing that a better evaluation of solvents removed from formulations. With the HT3 Headspace Analyzer one robust method may be applied to a variety of residual solvents. This application is directed to the initial identification of solvents and can also be used to quantify any solvents identified.

References

(1) USP <467> Residual Solvents and USP-NF Second Supplement <467>