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#102

Residual Solvent Analysis of Revised USP Methodology in a Fully Compliant 21 CFR 11 Headspace Analyzer

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BACKGROUND

After a long delay, the newly updated USP 467 method is now in effect. Used to monitor residual solvents in new and existing products, the new USP 467 method attempts to harmonize the European Pharmacopoeia (EP) with the USP method. The new method could potentially expand the list of solvents to be monitored to 53 and applies to all drug substances and products that utilize solvents in their manufacturing process.

The 53 solvents have been broken into three classes (I, II and III) based upon their toxicity or environmental impact with Class I solvents being the most toxic. In many ways, the testing has been simplified to include only static headspace parameters. Permissible Daily Exposure (PDE) limits have been established based upon a 10g daily dose. If all the raw materials used in manufacturing meet the maximum exposure limits, there is no need for additional testing if the daily dose is 10g or less. Also, if the Residual Solvent concentrations are known, the Residual Solvent concentration in the final product can be calculated based upon the formulation. If this is less than the exposure limit, no additional testing is required. If it is determined that the level is exceed, testing can be done to determine if the Residual Solvent concentration was reduced during the manufacturing process.

Many customers are coupling a static headspace analyzer with GC/MS, while others are using less expensive GC-FID detection with second column confirmation. For this paper, an EST Analytical Markelov HS9000 (Figure 1) was coupled to an Agilent 6890 GC with an FID detector.

EXPERIMENTAL

A series of standards were created in order to optimize the GC and Markelov HS9000 (Fig. 1) operating parameters.

The Class I standard (Restek cat # 36279) was prepared as follows:

1mL of Class I standard was added to a 100mL volumetric flask and then diluted with 9mL of dimethyl sulfoxide (DMSO), the flask was then brought to volume with reagent water and mixed. Next, 1mL of this standard was added to a 100mL volumetric flask and then brought to volume with reagent water and mixed. Next, 1mL of this standard was added to a 10mL volumetric flask and then brought to volume with reagent water and mixed. 1ml of the 10 ml solution was added to a 20 ml headspace vial containing 5 ml of reagent grade water. The vial was sealed and mixed prior to analysis.

The Class II A standard (Restek cat # 36271) was prepared as follows:

1mL of Class II A was added to a 100mL volumetric flask and then brought to volume with reagent water and mixed. 1ml of the solution was transferred to a 20 ml headspace vial containing 5 ml of reagent grade water. The vial was sealed and mixed prior to analysis.

Fig 1.- EST HS9000

The Class II B standard (Restek cat # 36280) was prepared as follows:

1mL of Class II B was added to a 100mL volumetric flask and then brought to volume with reagent water and mixed. Five ml of the solution was transferred to a 20 ml headspace vial containing 1 ml of reagent grade water. The vial was sealed and mixed prior to analysis.

The Markelov HS9000 equipped with the static volume controlled injection system containing a 1 ml sample loop was utilized to generated results following procedure A and B of the method. The results generated by equilibrating the standards for 45 minutes at 80°C while mixing with the horizontal rotary evaporation technique. The headspace of the sample vial containing 6mL of standard was pressurized to 10psi and reduced to 7psi to fill the sample loop. The sample vial was maintained at 80°C during this pressurization / loop fill process. The 1 ml sample loop was back-flushed with GC carrier gas for 1 minute to introduce the sample to the GC inlet. The Headspace and GC conditions for the analyses are shown in Table 1. Chromatograms for each class on the Rtx- 624 column can be seen Figures 2-6.

Column1	EST Markelov HS9000	Column2	Agilent 6890/FID	Agilent 6890/FID3
	Procedure A & B		Procedure A	Procedure B
Sample Size	6mL	Column	RTx-624 (G43)	Stabilwax (G16)
Sample Platen Temp	80° C	Column Length	30 M	30 M
Equilibration Time	45 minutes	Column Diameter	0.32 mm	0.32 mm
Valve Oven Temp	120° C	Film Thickness	1.8 um	0.25 um
Transfer Line Temp	125° C	Carrier Gas	Helium	Helium
Mixing Mode	Horizontal Rotary	Column Flow	2.15 mL/min	2.15 mL/min
Sample Vial Pressure	10psi	Mode	Constant Flow	Constant Flow
Loop Fill Pressure	7psi	Split Ratio	5:01	5:01
Inject Time	1 minute	Inlet type	Split/Splitless EPC	Split/Splitless EPC
Inject Volume	1mL	Inlet Temp	140° C	140° C
		Initial Oven Temp	45° C	50° C
		Restek Column Cat #	10970	10970
		Restek Inlet Liner Deactivated	1mm (# 36271)	1mm (# 36271)

Table 1 – Optimized GC and Headspace parameters for USP 467 analysis.

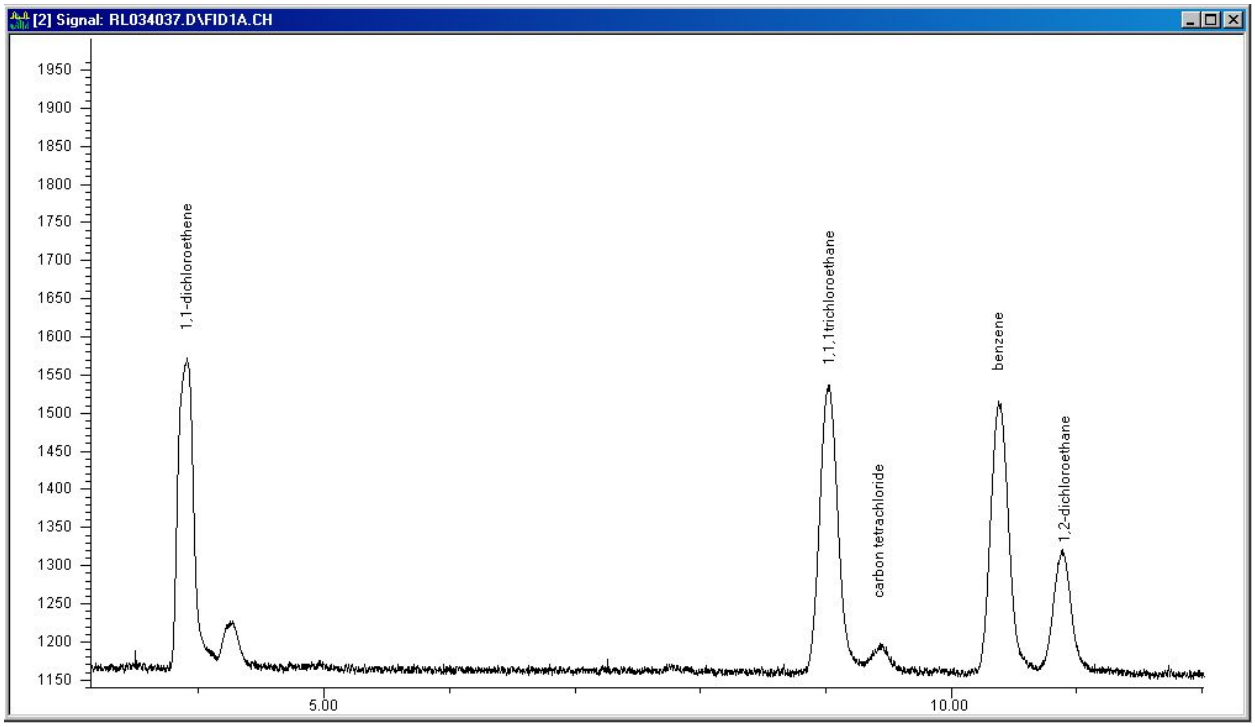

Figure 2 – FID Chromatogram of Class I Solvents on Restek's Rtx-624 column

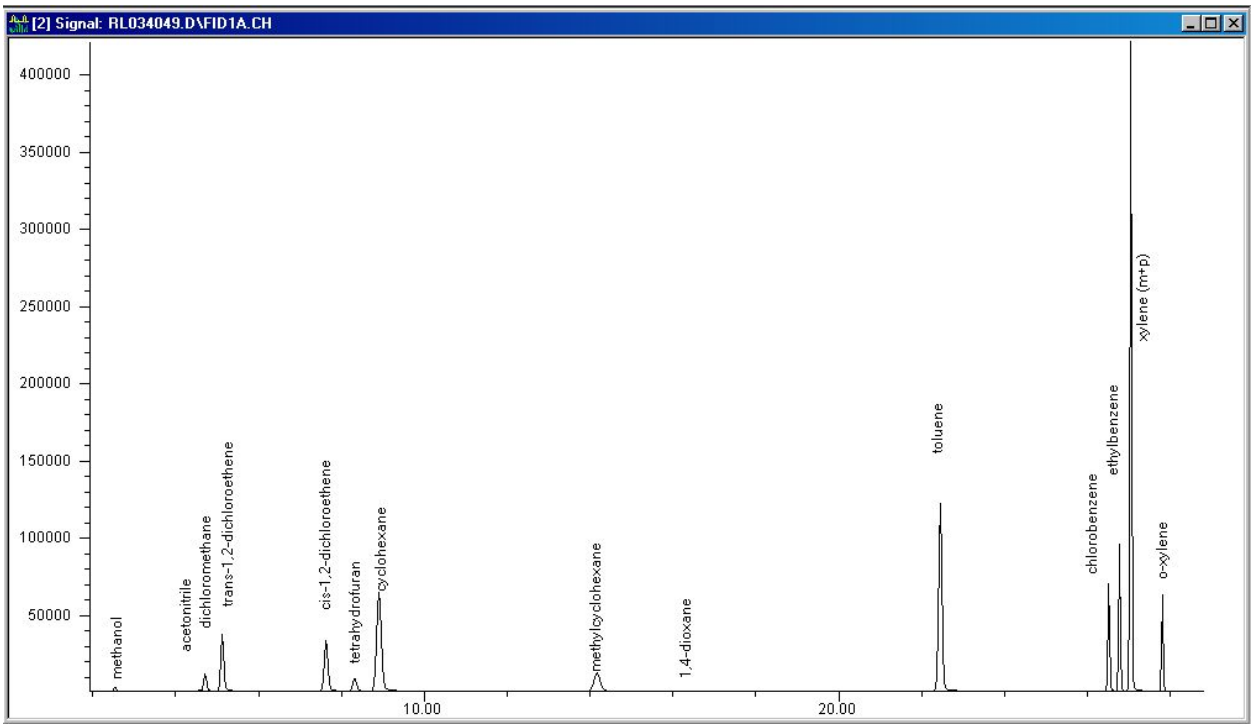

Figure 3 – FID Chromatogram of Class II A Solvents on Restek's Rtx-624 column

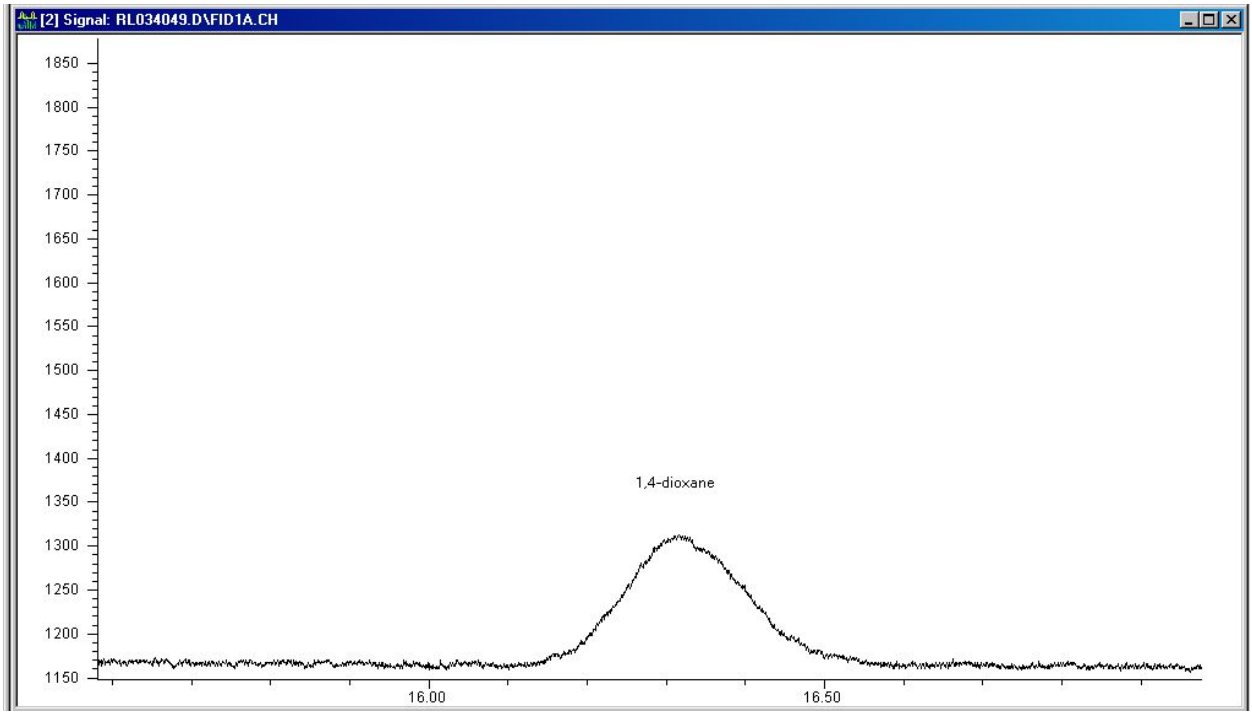

Figure 4 – A zoomed in FID Chromatogram of 1,4-dioxane from the Class II B Solvent list on Restek's Rtx-624 column

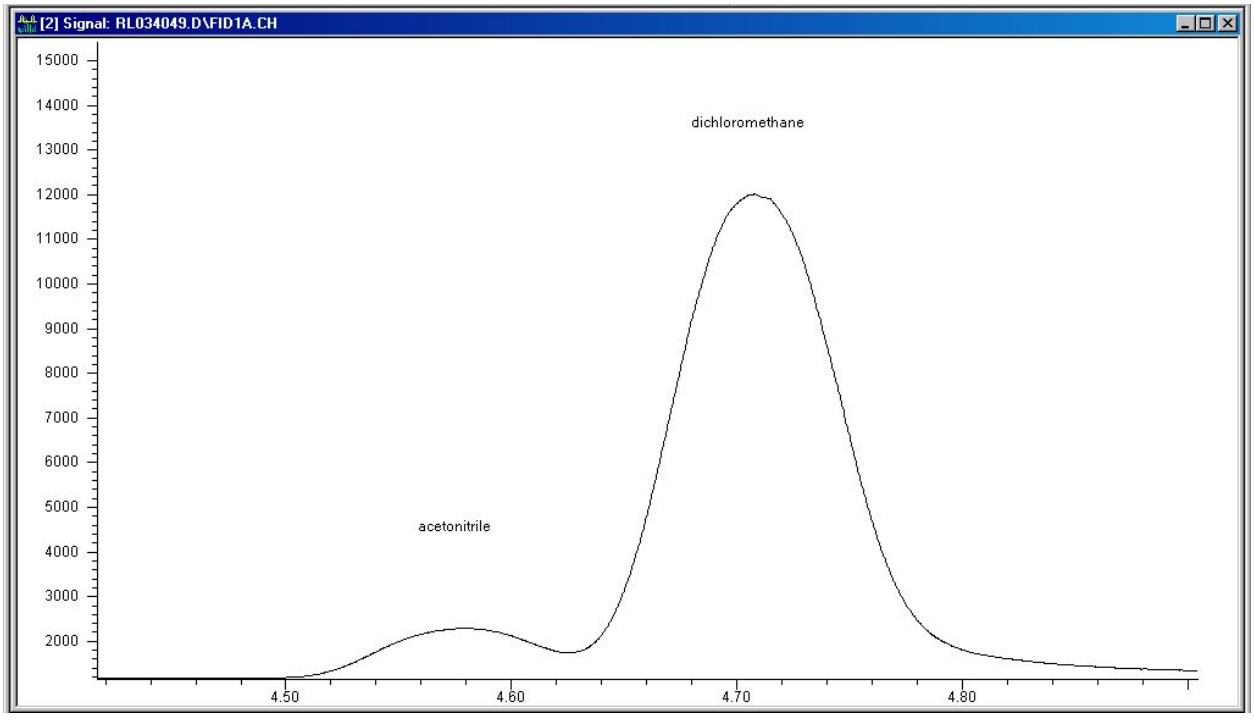

Figure 5– FID Chromatogram of Class II A Solvents on Restek's Rtx-624 column showing separation of Acetonitrile and Dichlormethane .

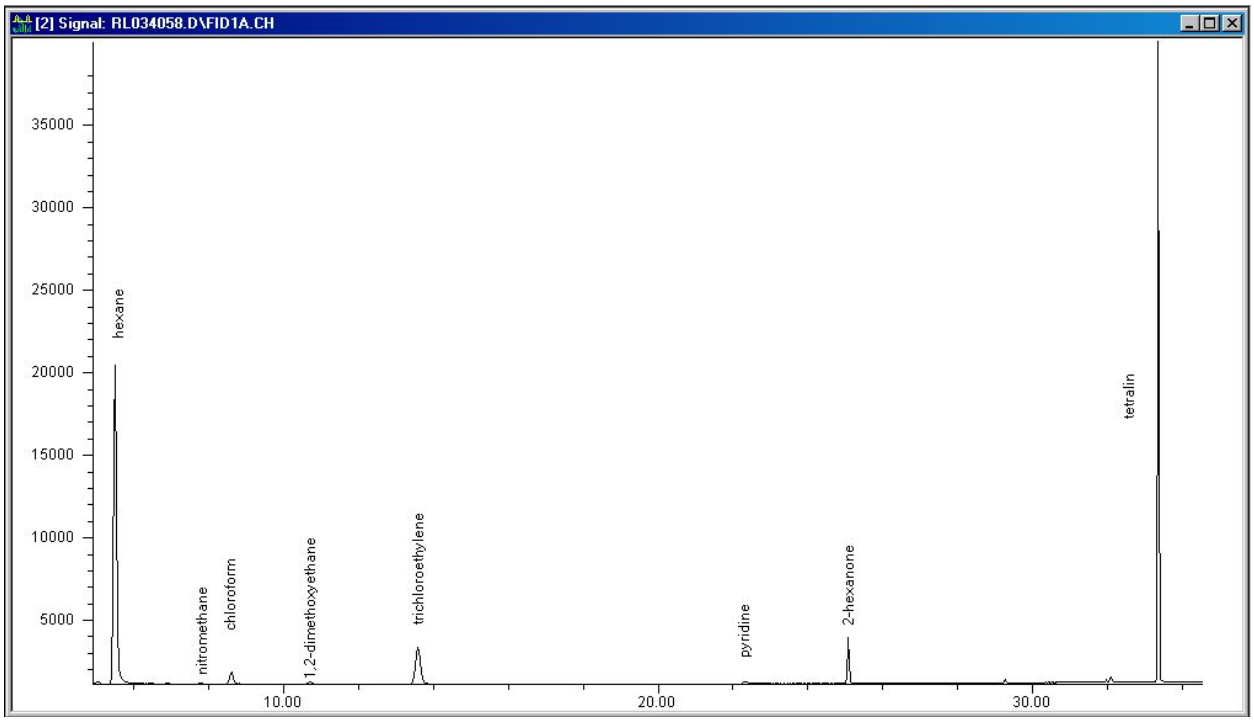

Figure 6 – FID Chromatogram of Class II B Solvents on Restek's Rtx-624 column

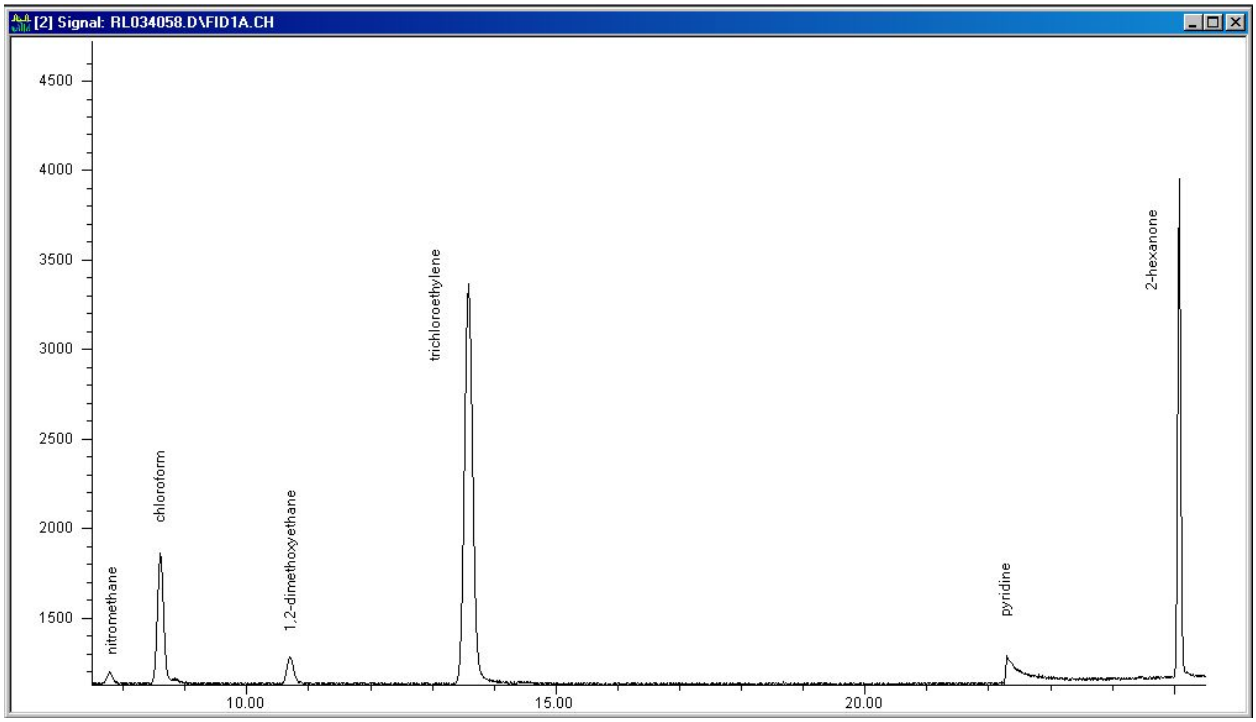

Figure 7 – A zoomed in FID Chromatogram of Class II B Solvents on Restek's Rtx-624 column

If a peak matched the retention time of the standard, the residual solvent must be verified by detection on a secondary column. In this case, we utilized a Stabilwax® 30m, 0.32mm ID, 0.25 from Restek Corporation (See figures 7-11). If a Residual Solvent is verified, the solvent must be quantified on either of the two columns used for analysis, whichever gives the better result.

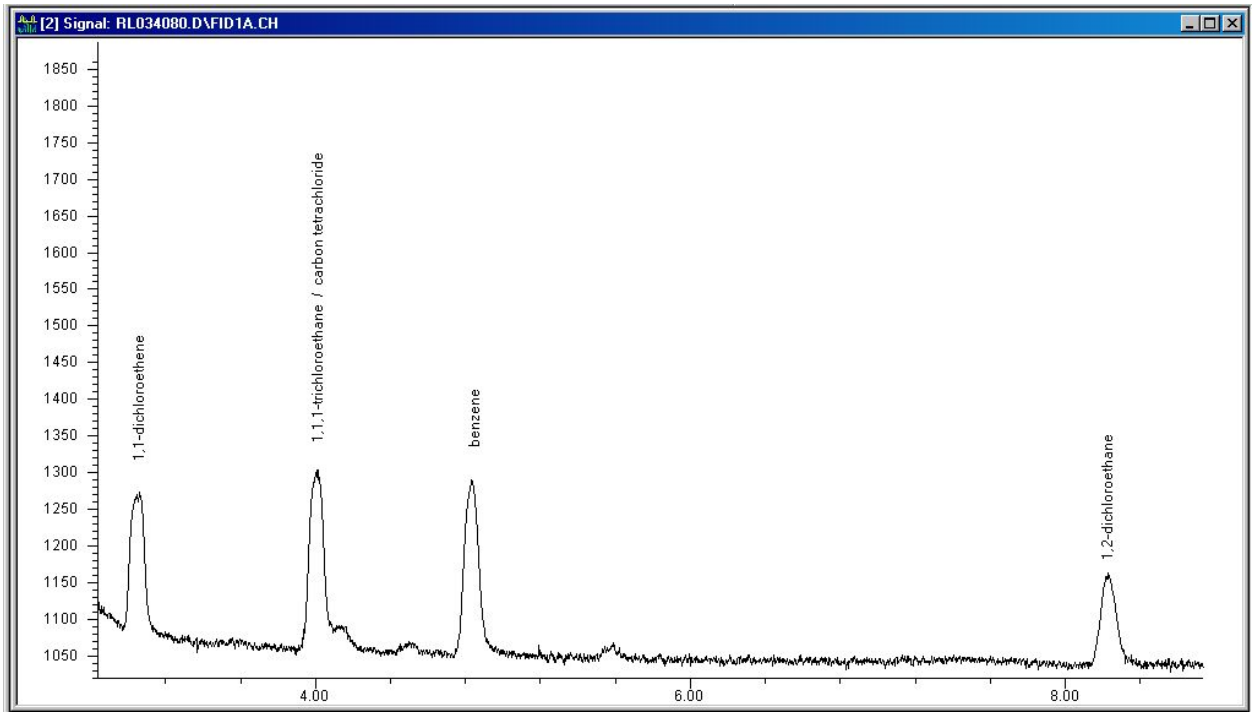

Figure 8 – FID Chromatogram of Class I Solvents on Restek's Stabilwax column

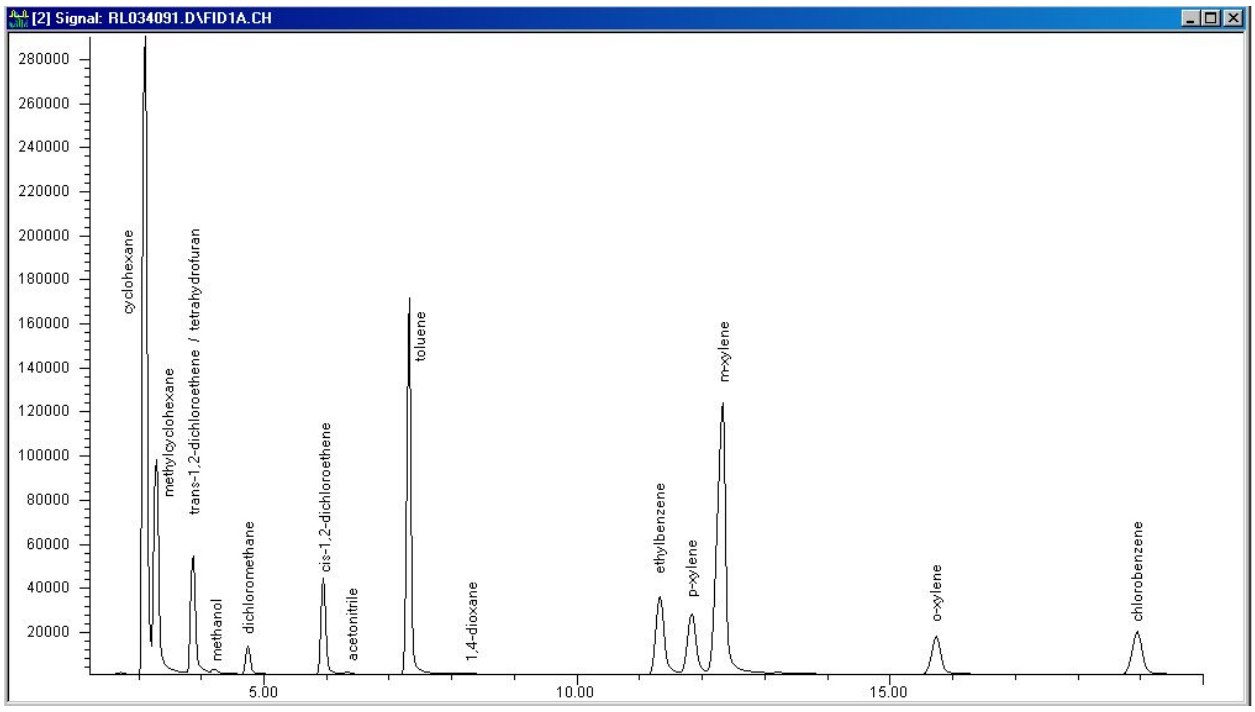

Figure 9 – FID Chromatogram of Class II A Solvents on Restek's Stabilwax column

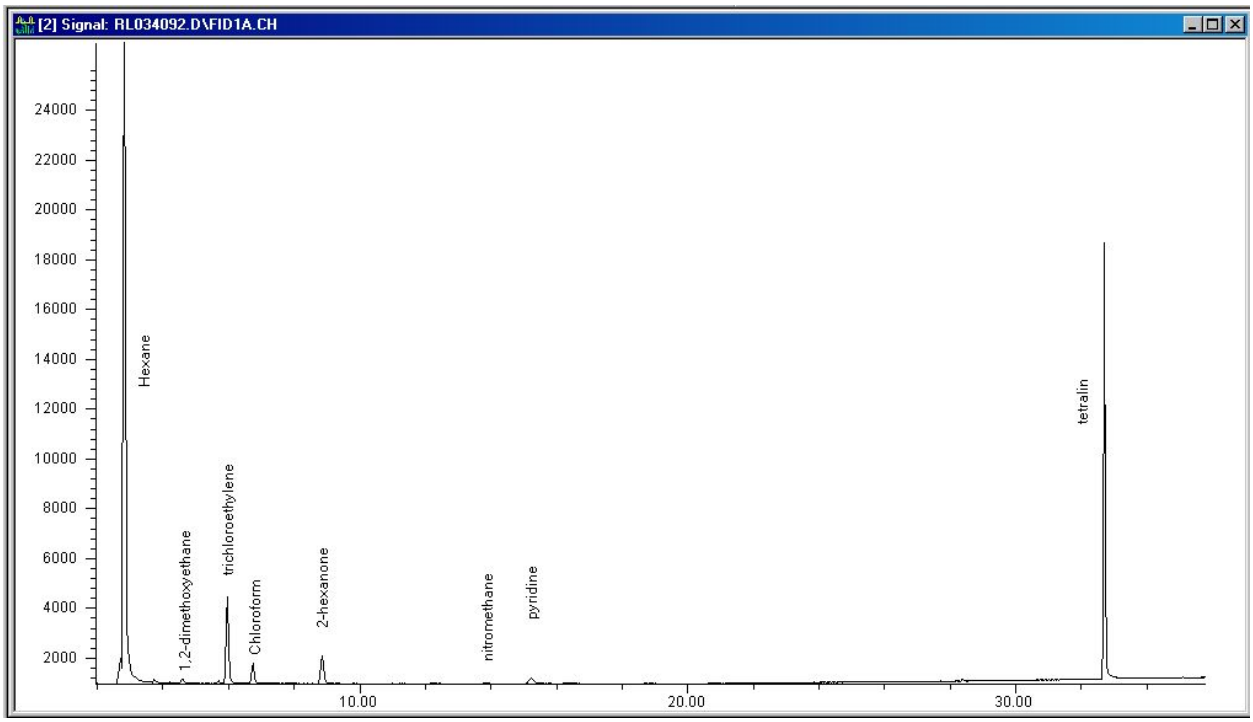

Figure 10 – FID Chromatogram of Class II B Solvents on Restek's Stabilwax column

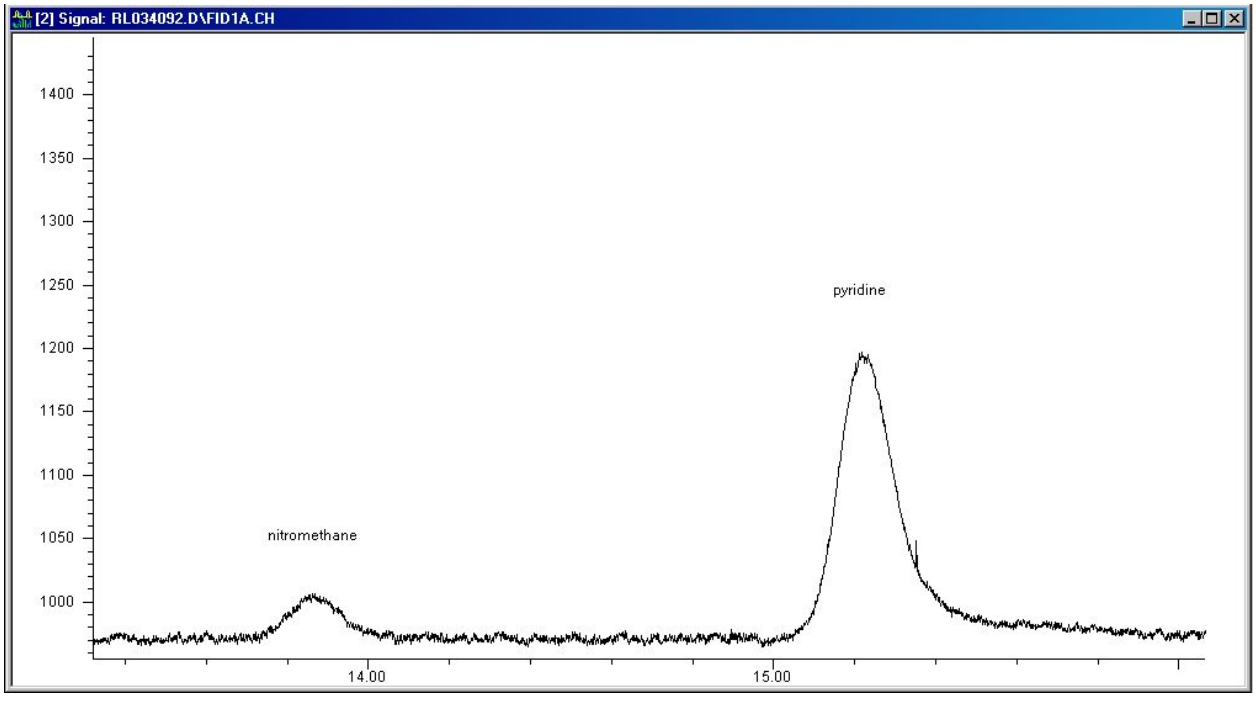

Figure 11 – A scaled FID Chromatogram of Class II B Solvents on Restek's Stabilwax column

The Markelov HS9000 headspace analyzer has the capability to provide automated method development which can be extremely useful when creating a new optimized method. Any parameter, (equilibration time, temperature, pressure, etc) can be automatically incremented by a user defined amount and a series of runs performed. The user can easily look through the analytical results to see which parameters gave the best results.

The Markelov HS9000 also implements a 21 CFR 11 reporting function where the user can define a set of parameters they wish to report (injection time, temperature, pressure, etc) and these results can be stored and sent to any system on the network. An example of this report is below.

SEQUENCE	RUN	REPORT CFR-21 Compliant		11/11/2008	5:40:30
SEQUENCE	STARTED				
Username:	Administrator				
Current	Date:	11/11/2008 5:40:30	PM		
Sequence:	USP467				
Total	Samples:	2			
Sample:	#1				
Sample	Mode:	Loopfill			
Method:	USP467	LF			
Sample	Equilibration	Start: 11/11/2008	5:45:56	PM	
Sample	Equilibration	End: 11/11/2008	6:32:02	PM	
Sample	Equilibration	Elapsed: 46:m	6:s		
Sample	Injected:	11/11/2008 6:33:05	PM		
Vial	Pressure	Actual: 10	PSI		
Loop	Pressure	Actual: 7.1	PSI		
Platen/Vial	Temperature:	81 C			
Valve/Loop	Temperature:	121 C			
Line	Temperature:	125 C			
GC	Start	Sent: 11/11/2008	6:33:05	PM	
Sample:	#2				
Sample	Mode:	Loopfill			
Method:	USP467	LF			
Sample	Equilibration	Start: 11/11/2008	6:54:15	PM	
Sample	Equilibration	End: 11/11/2008	7:40:19	PM	
Sample	Equilibration	Elapsed: 46:m	4:s		
Sample	Injected:	11/11/2008 7:41:21	PM		
Vial	Pressure	Actual: 10	PSI		
Loop	Pressure	Actual: 7	PSI		
Platen/Vial	Temperature:	81 C			
Valve/Loop	Temperature:	123 C			
Line	Temperature:	126 C			
GC	Start	Sent: 11/11/2008	7:41:21	PM	
SEQUENCE	COMPLETED				
Username:	Administrator				
Current	Date:	11/11/2008 7:42:24	PM		
Sequence:	USP467				
Total	Samples:	2			
Start	Date:	11/11/2008 5:40:30	PM		
Elapsed	Time:	2:h 1:m	54:s		

Conclusion

Initial set up of this method can be difficult if the system is not optimized for separation and reproducibility. The Markelov HS9000, with its ability to automatically perform a variety of unattended analyses to optimize a given set of parameters, makes the set up much easier to perform. This ability, along with the reporting functions makes the Markelov HS9000 an impressive tool for this analysis.

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