APPLICATION NOTE

Gas Chromatography

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Residual Solvents in Pharmaceuticals by USP Chapter <467> Methodology

Introduction

The synthesis of active pharmaceutical ingredients (API) may require multiple reaction steps that produce undesirable reaction byproducts or utilize various solvents that have to be removed from the finished product. These solvents and byproducts may be measured with headspace gas chromatography for those volatile residual organic solvents according to the USP chapter 467 method. Method USP 467 classifies residual solvents into three classes according to toxicity; class 1 solvents are to be avoided unless there is strong justification, class 2 solvents are those that should be limited due to toxicity concerns.

The allowable concentration limits for each solvent vary in response to their respective toxicity. The varied concentration and detector response results in chromatography with many varied peak heights that require reliable integration without detector saturation.

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Experimental

A PerkinElmer Clarus® 690 gas chromatograph and TurboMatrix™ headspace sampler was used for the separation of residual solvents according to USP 467. Instrument control and data analysis was through Waters® Empower® 3 software. The headspace conditions described in Table 1 were taken from the USP method. The TurboMatrix HS is a pressure-balanced headspace sampler; the basis of sample collection in this system is a calculation of sample volume, allowing gas at a known flow rate to enter the analytical column for a specific time.

Experimental Conditions

The experimental conditions for the headspace method are described in Table 1 with the new Flame Ionization Detector (FID) conditions shown in Figure 1. The new narrow jet uses less hydrogen than previous designs and the increased maximum attenuation to 64 enables the wider analytical range of the 690 series. The GC conditions are taken from the USP 467 method and are shown in Table 2.

Results

Procedure A was used to identify the residual solvents in a pharmaceutical sample. In this, all solvents are initially analyzed using the G43 column and associated GC conditions. The class two solvents are subdivided into class 2A and class 2B. Class 1 analytes are prepared following procedure A in method USP 467 with sequential dilutions with a 1 mL volume of the final dilution then added to 5 mL of water in the vial as described in the method. The concern with class 1 solvents is toxicity and a S/N of greater than five is required for 1,1,1-trichloroethane with the remaining analytes having a S/N greater than three. Such calculations are achieved through the software from a selected region of noise close to the analyte of interest. The analytes are identified in Figure 2 and all exceed the SN required by the method demonstrating the new FID performance.

The additional system suitability for the method requires a resolution of greater than 1 between acetonitrile and methylene chloride. The dilutions for the class 1 solvent under USP 467 describe a dilution of 1:1000 between dilution 1 and 3. The wide range FID allows for quantification of these analytes using the maximum signal attenuation. The analysis of the class 1 standards is shown with attenuation 1 in Figure 2 and 3 and attenuation 64 in Figure 4.

Table 1. Detailed Headspace Analytical Conditions.

Headspace Unit	PerkinElmer TurboMatrix HS-40
Headspace Mode	Constant
Needle Temperature	105 °C
Transfer Line Temperature	110 °C
Oven Temperature	80 °C
Thermostat Time	20 min
Vial Pressurization Time	1.0 min
Withdraw Time	0.1 min
Injection Time	0.04 min
Column Pressure	12 psig
Injection Pressure	15 psig
Vial Pressure	15 psig
Vial Vent	On
Transfer Line	Fused Silica (0.320 mm)

Table 2. Gas Chromatograph Analytical Conditions taken from the USP 467 method.

Column	624 phase 30 M x 0.32 mm X 1.8 µm		
Carrier	Helium at 35 cm sec^{-1} split at 1:5		
Capillary Injector	140 °C		
FID	250 °C		
GC Oven Program	Initial	Ramp	Final
	40 °C (20 min)	20 °C/min	240 °C (20 min)

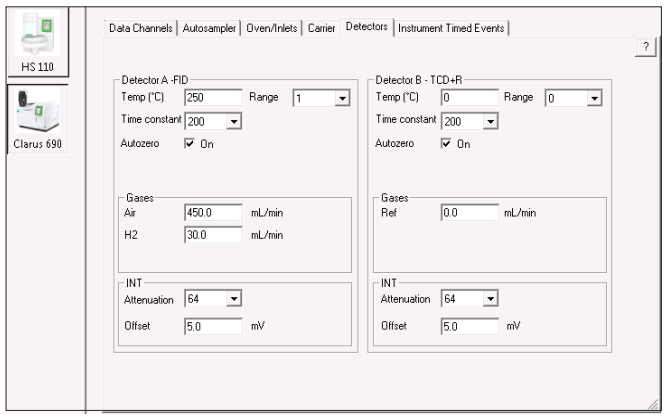

Figure 1. New wide range Flame Ionization Detector showing air hydrogen mix and wide range attenuation.

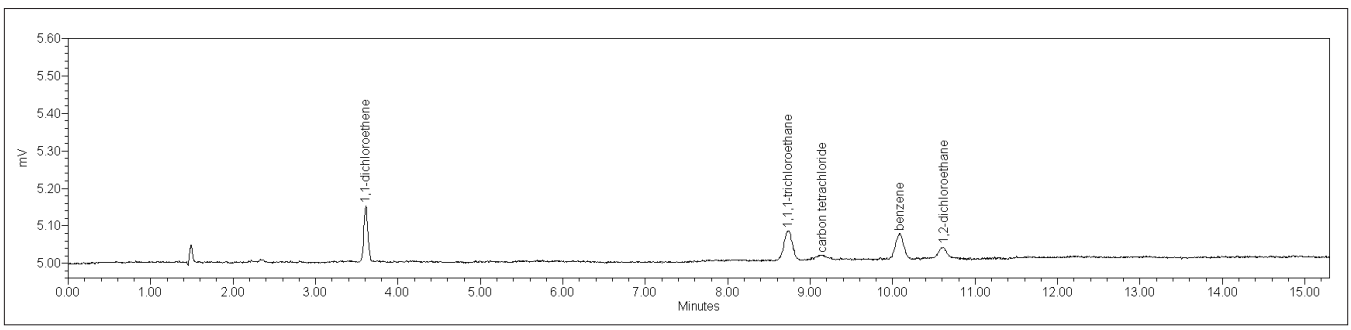

Figure 2. Class 1 solvents with FID at attenuation 1, the analytes are present at the system suitability limit demonstrating that the S/N exceeds the method requirements.

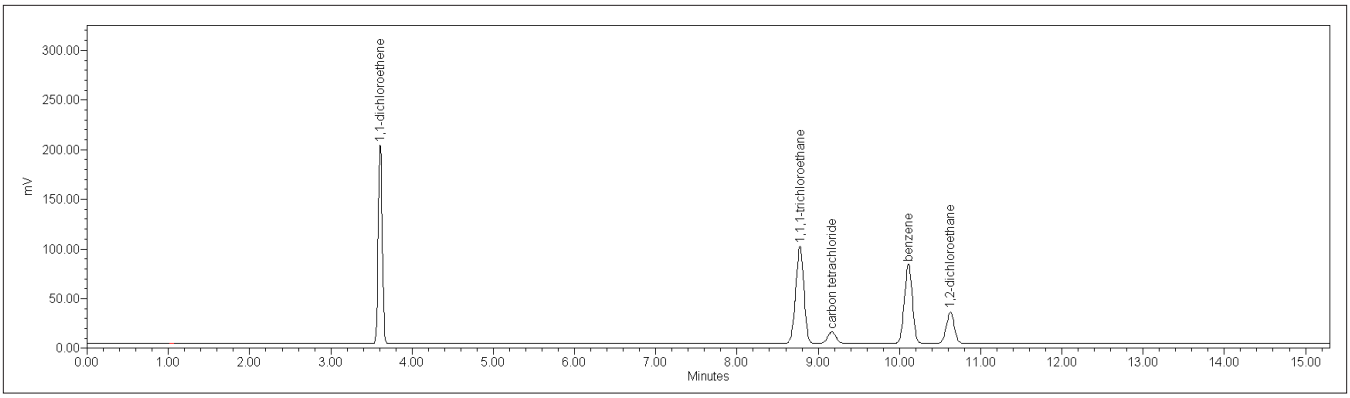

Figure 3. Class 1 solvents with FID at attenuation 1, the first of the three dilutions is shown to demonstrate that the operational range of the FID is not easily saturated, 1,1-dichloroethene is at a concentration of 400 ppm.

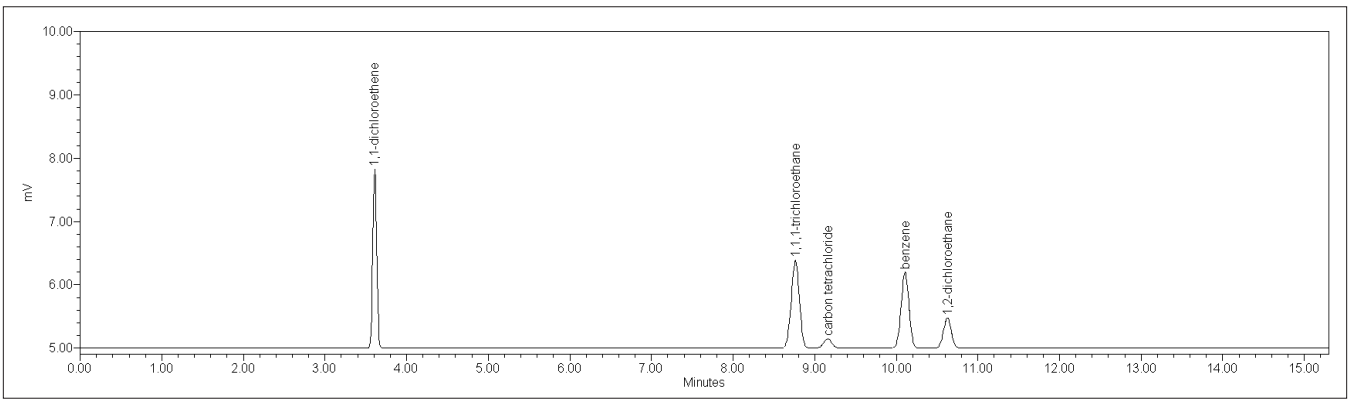

Figure 4. Class 1 solvents with FID at attenuation 64 the first of the three dilutions is shown to demonstrate that the operational range of the FID is not easily saturated, 1,1-dichloroethene is at a concentration of 400 ppm.

The class 2A solvents are shown in Figure 5 and Figure 6 with class 2B solvents shown in Figure 8 and Figure 9.

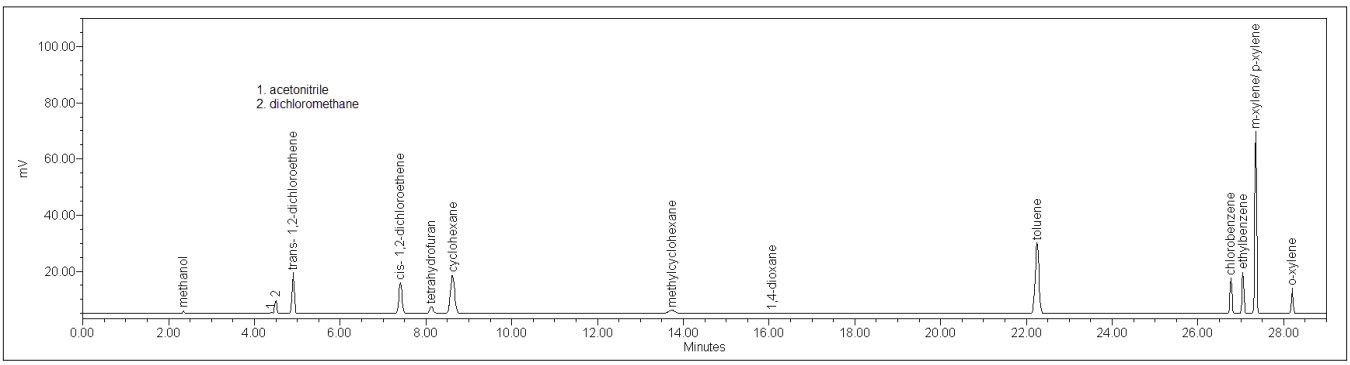

Figure 5. Class 2A solvents at attenuation 1.

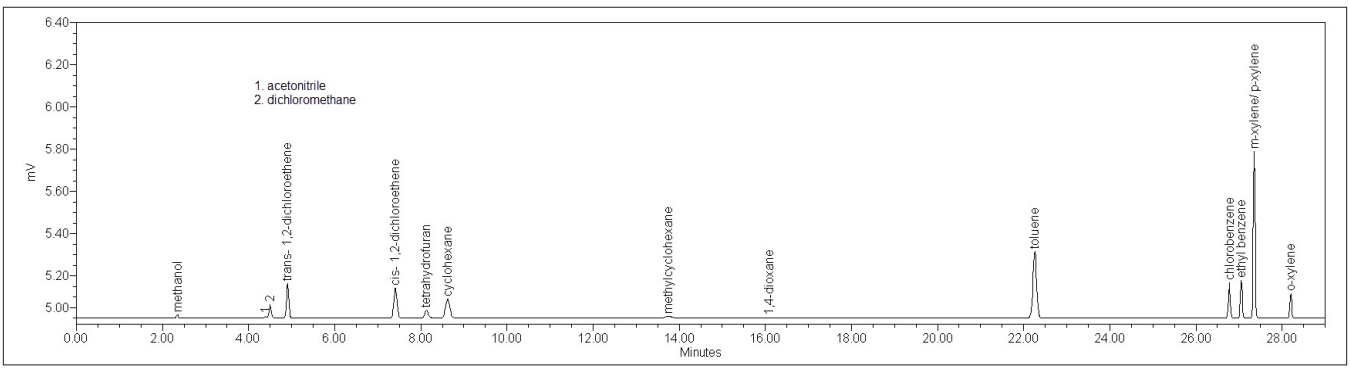

Figure 6. Class 2A solvents at attenuation 64.

The resolution of the acetonitrile and methylene chloride critical pair shown in Figure 7, exceeds the method criteria.

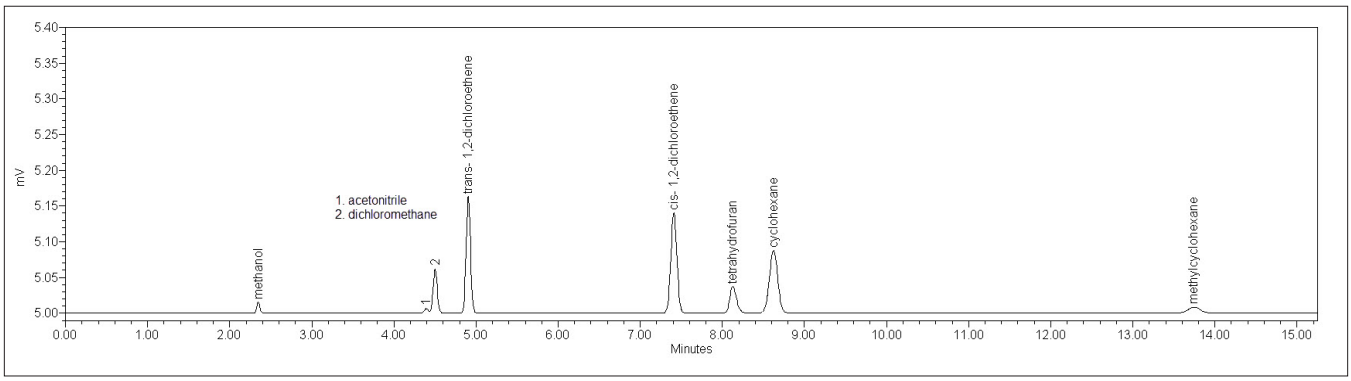

Figure 7. The resolution between acetonitrile and methylene chloride exceeds method criteria at attenuation 64.

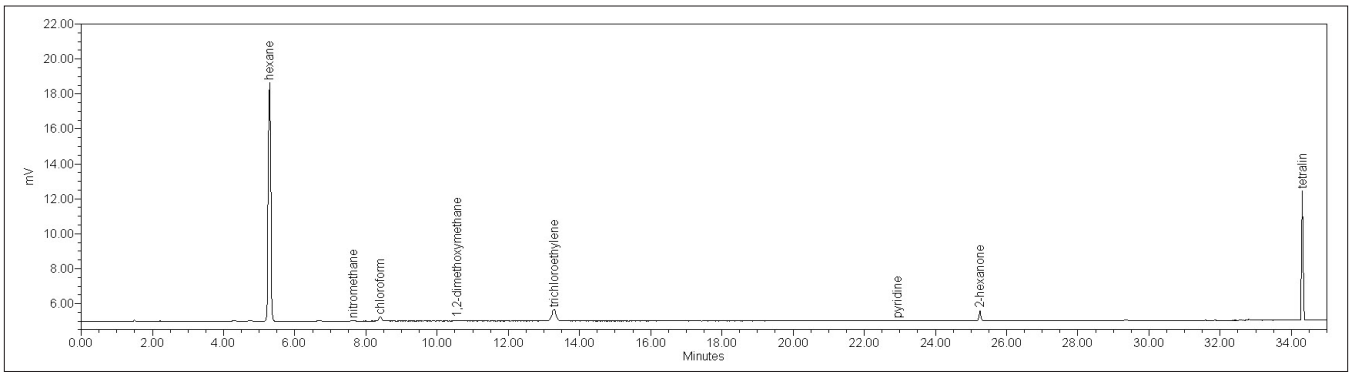

Figure 8. Class 2B solvents at attenuation 1.

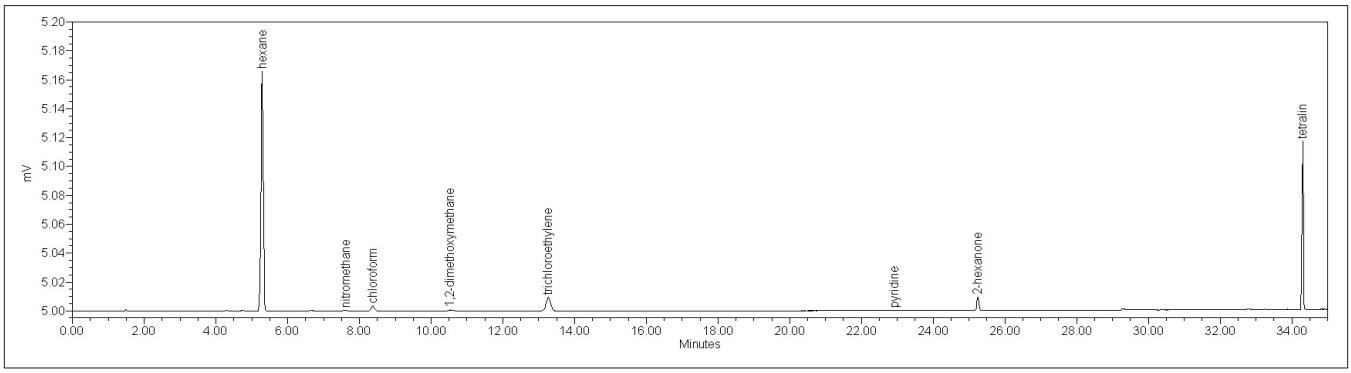

Figure 9. Class 2B solvents at attenuation 64.

All solvent mixes are shown at the method described quantification level.

A representative mixture was created methanol, benzene, toluene, dichloromethane and hexane in the following concentrations; methanol 3000 ppm, benzene 1 ppm, dichloromethane 600 ppm, hexane 290 ppm and toluene 890 ppm to demonstrate the FID performance at what are the concentration limits for these solvents.

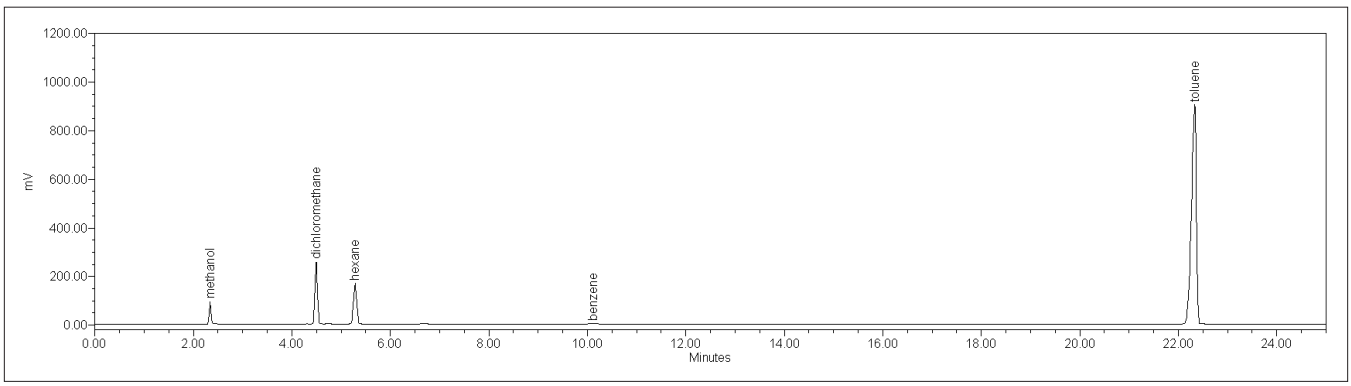

Figure 10. Five solvents at their respective limit concentrations detected with an attenuation setting of one.

As can be seen from Figure 10 the response from toluene is in excess of 800 mV and is approaching the detector saturation point, The peak for benzene is shown in Figure 11 after zooming in on the chromatogram.

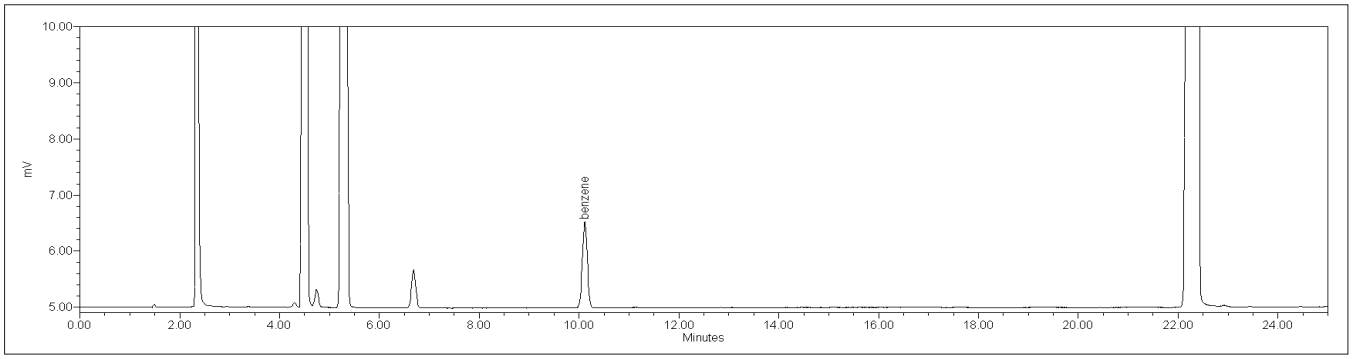

Figure 11. Close up of the created solvent mixture at the allowable concentrations to show the benzene peak in more detail.

The same sample with the expanded integration option allows for the quantitation of solvents that are greater than the permissible values as can be seen in Figure 12.

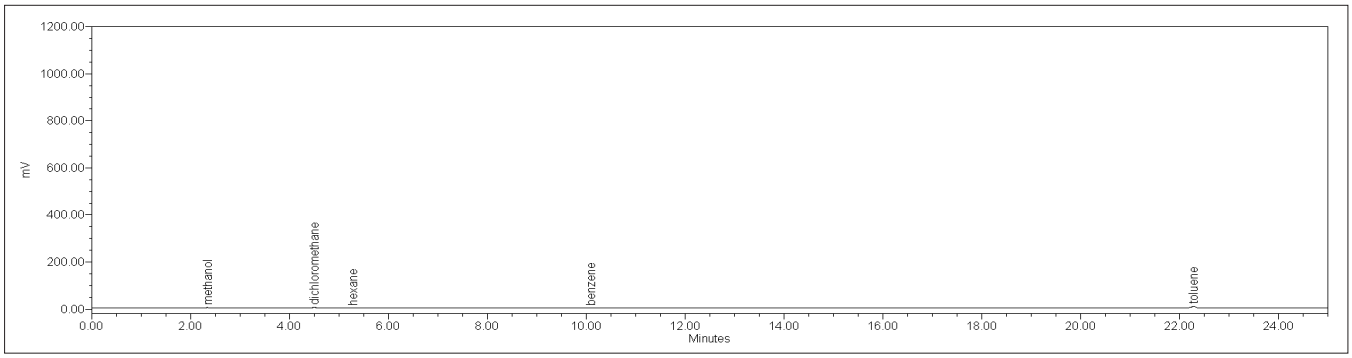

Figure 12. Previously described solvents at the allowable limit concentrations with the detector attenuation now at 64.

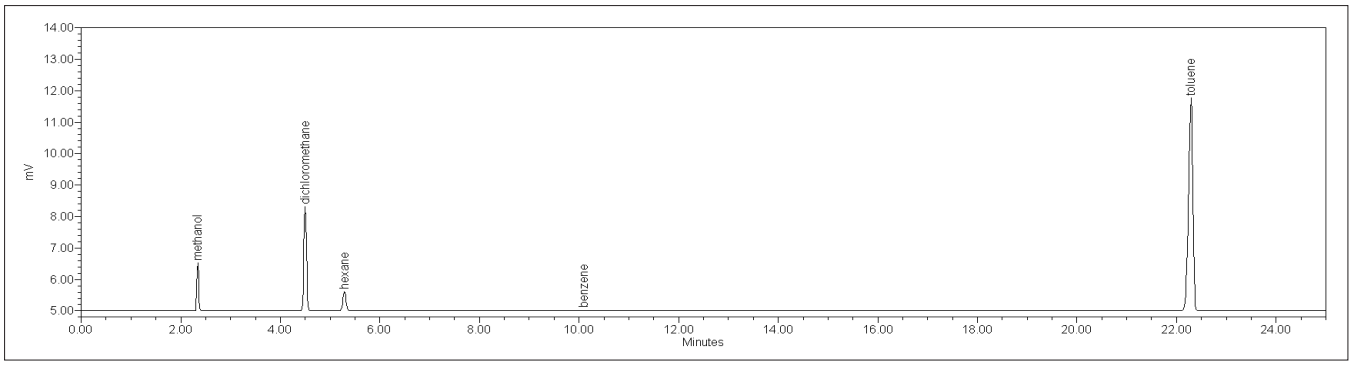

Figure 13. Five compounds present at limit concentration with attenuation 64.

Further examination of the data (Figure 14) shows that the sensitivity of FID has not been compromised with the benzene still easily detected at the 1 ppm concentration.

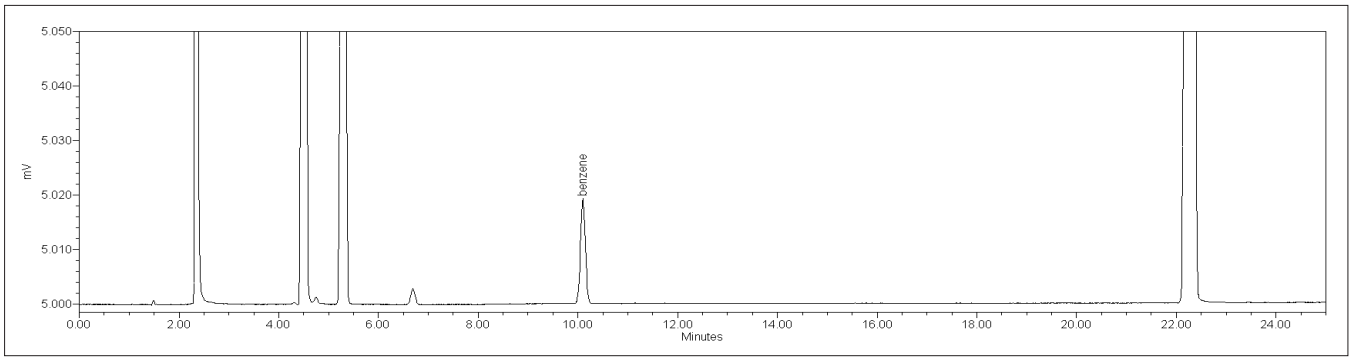

Figure 14. Benzene response is still sensitive (S/N 1291) at the 1 ppm concentration using attenuation 64.

Conclusions

The Clarus 690 and TurboMatrix headspace autosampler exceed the requirements for USP 467 and can be fully utilized through the Waters® Empower® 3 software. The new wide range amplifier has sufficient sensitivity to satisfy the S/N requirements and a large dynamic range that reduces the need for repeat analysis of solvents of unknown concentration that could potentially saturate other detector options.

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