Residual Solvents Analysis: Satisfying USP 467 Using a New Benchtop Time-of-Flight Mass Spectrometer

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Introduction

Pharmaceutical manufacturers are responsible for testing the safety and purity of their products before sending them out to market. One major test method from the United States Pharmacopeia, USP 467, lays out the risk classification and testing procedures for determining the concentration of over 50 residual solvents that are known human carcinogens or environmental hazards in final pharmaceutical products. Time-consuming and fraught with the possibility of false positives, the current method calls for a gas chromatograph coupled to a flame-ionization detector (GC-FID) to confirm the identity of solvents based only on the retention time of standards with multiple column sets and multiple runs required for each set of solvents. Here, we propose the use of GC-TOFMS with patented deconvolution algorithms to eliminate the need for multiple runs with different GC columns, thus increasing throughput. The use of GC-MS also eliminates the potential for false positives, while also providing the ability to monitor for any potentially unexpected contaminants.

Methods

One combined standard mix was made up at the concentration limit as calculated from Permitted Daily Exposure (PDE) in USP 467 of each Class 1 and 2 residual solvents from commercial mixes purchased from Sigma Aldrich. An over-the-counter, generic ibuprofen sample was prepared according to USP 467 and spiked with 1.5X the concentration limit of Class 2A residual solvents.

Gas Chromatograph	Agilent 7890 with LECO L-PAL3 Autosampler
Injection	1mL HS injection, 30 s agitation at 80 °C, split 50:1 @ 200 °C
Carrier Gas	He @ 1.5 mL/min, Constant Flow
Column	Rxi-624SilMS, 30 m x 0.25 mm i.d. x 1.4 µm coating (Restek, Bellefonte, PA, USA)
Oven Program	35 °C (1 min), to 250 °C @ 25 °C/min (5 min)
Transfer Line	280 °C
Mass Spectrometer	**LECO Pegasus® BT**
Ion Source Temperature	250 °C
Mass Range	15-650 m/z
Acquisition Rate	10 spectra/s

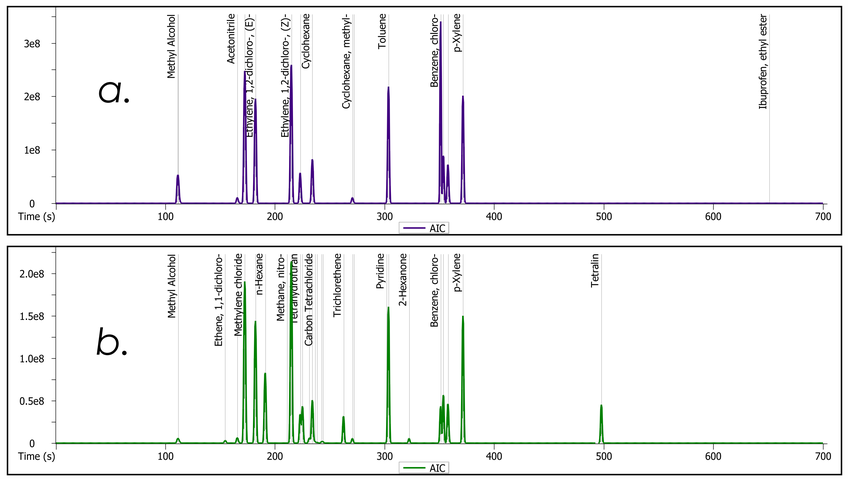
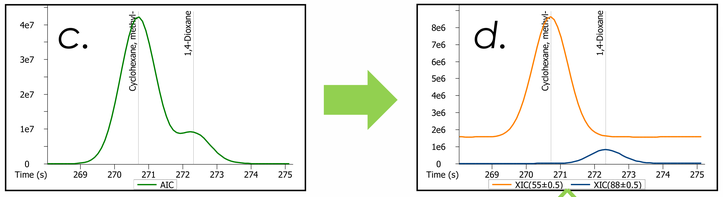


Figure 1: a) Chromatogram of ibuprofen sample spiked with Class 2A Residual Solvents at 1.5X greater than the specified concentration limit;

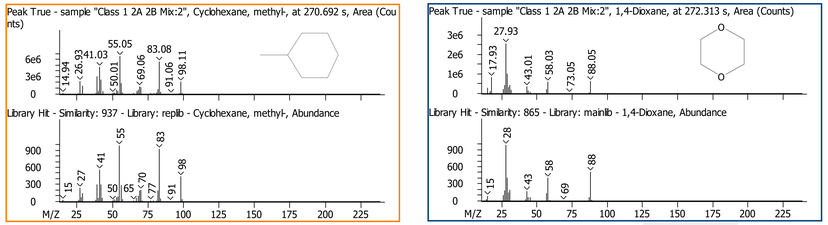
b) Chromatogram of the combined Class 1, 2A, and 2B Residual Solvents standard is shown above, with peak markers displayed for each analyte of interest found using Target Analyte Find;



c) The zoomed inset shows a coelution of Methylcyclohexane and 1,4 Dioxane, which would not be fully resolved for quantification by FID;

d) Traces of the characteristic mass for each of the analytes, m/z 55 and m/z 88 respectively, clearly show two distinct peaks;

e) High Spectral Similarity Scores provide confident identification of each compound, with masses properly apportioned to each Peak True spectra using NonTarget Deconvolution™.



Tables 1-3: Class 1, 2A, and 2B Residual Solvents are listed with concentration limits as specified by USP 467 and Retention Times used for target identification.

Table 1: Class 1 Residual Solvents

Solvent	R.T. (s)	Concentration Limit (ppm)
Ethene, 1,1-dichloro-	154.612	8
Ethane, 1,1,1-trichloro-	231.419	1500
Carbon Tetrachloride	236.519	4
Benzene	242.619	2
Ethane, 1,2-dichloro-	243.82	5

Table 2: Class 2A Residual Solvents

Solvent	R.T. (s)	Concentration Limit (ppm)
Methyl Alcohol	111.509	3000
Acetonitrile	165.613	410
Methylene chloride	172.514	600
Ethylene, 1,2-dichloro-, (E)-	182.215	1870
Ethylene, 1,2-dichloro-, (Z)-	214.917	
Tetrahydrofuran	223.118	720
Cyclohexane	234.119	3880
Cyclohexane, methyl-	270.722	1180
1,4-Dioxane	272.322	380
Toluene	303.624	890
Benzene, chloro-	351.228	360
Ethylbenzene	353.728	
m-Xylene	357.929	2170
p-Xylene	371.63	

Table 3: Class 2B Residual Solvents

Solvent	R.T. (s)	Concentration Limit (ppm)
n-Hexane	191.115	290
Methane, nitro-	211.217	50
Chloroform	225.118	60
Ethane, 1,2-dimethoxy-	238.419	100
Trichlorethene	262.621	80
Pyridine	301.624	200
2-Hexanone	322.426	50
Tetralin	497.94	100

Conclusion

A HS-GC-TOFMS method has been developed for the quick screening of Class 1 and 2 Residual Solvents, identifying and providing tentative quantitation for each analyte. Proof-of-concept was tested using spiked commercially available ibuprofen, yielding preliminary results in less than 10 minutes.

Delivering the Right Results