The Analysis of Synthetic Drugs of Abuse by GC-VUV

APPLICATION NOTE

Introduction

The use of synthetic drugs of abuse by Americans of all age demographics has led to thousands of hospitalizations and overdose deaths over the past several years. These compounds are sold by international manufacturers and imported legally into America because the synthesis of banned substance variants outpaces the U.S. DEA's ability to identify them. This rash of designer drug overdoses highlights the value of being able to decipher between the subtle chemical bond differences inherent to synthetic drug variants. Forensic scientists have struggled in the positive identification of synthetic opioid, amphetamine, cathinone, benzodiazepine, and cannabinoid isomers. Characterization of these compounds by GC-MS can be problematic because of the difficulty in forming useful molecular ions and generating mass spectra that can differentiate between structural isomers.

GC-VUV provides a robust analytical alternative capable of the rapid identification and quantitation of these drugs of abuse. The VGA universal gas chromatography detector delivers excellent measurement sensitivity and unmatched selectivity without the need for chromatographic baseline resolution or continuous calibration.

Most compounds absorb strongly in the VUV spectrum, and their inherent absorbance cross sections lead to unique spectral fingerprints. GC-VUV data is inherently three dimensional and specific to compound chemical structure, allowing some of the separation to occur at the detector. This effectively means that standard analyses which previously required complex chromatographic separation can be simplified and shortened due to the ability to deconvolve overlapping spectral responses.

VUV absorbance spectra are typically highly structured and distinct for individual compounds, yet exhibit the intuitive property of having similar features when measuring related compound classes. VUV spectroscopy is a non-destructive technique that complements mass spectrometry by providing consistent compound characterization irrespective of isomeric equivalencies or the ability to ionize. As is demonstrated in the following examples, definitive identification and quantitation of drug isomers by GC-VUV can typically be achieved in less than 15 min.

Experimental

- Instrumentation and Standards

GC-VUV analysis was completed with the following setup:

Detector: VUV Analytics VGA-100

Gas Chromatograph: Agilent 6890 equipped with a 7683 model autosampler

Columns: Restek Rxi-5ms (30 m x 0.25 mm ID x 0.25 µm). Cathinone and amphetamine data in Fig. 5 and 6 used Agilent HP-5 (30m x 0.32mm x 0.25 µm).

Carrier Gas: H_2 at 2.0 mL/min. Cathinone and amphetamine data in Fig. 5 and 6 used H_2 at 5.0 mL/min.

VUV ANALYTICS

Injector: Split: 10:1 250°C. Cathinone and amphetamine data in Fig. 5 and 6 used splitless injection.

Injection volume: 1.0 µL

Oven profile: 80°C (hold 1.0 min); ramp 30°C/min to 350°C, (hold 5.0 min). Cathinone and amphetamine data in Fig. 5 and 6 used 50° C (hold 1 min); ramp 15°C/min to 150°C.

Make-up gas: N_2, 0.250 psi

Synthetic drugs of abuse standards were supplied at 1000 ppm concentration unless otherwise noted. Fentanyl was received as 100 ppm and flubromazolam as 500 ppm. All analyzed samples were dissolved in methanol, and single component standards were diluted as noted. Parafluorofentanyl, valeryl fentanyl, furanyl fentanyl, para-methoxyamphetamine, para-methoxymethamphetamine, and 3,4-MDMA were all diluted to 333 ppm.

Results and Discussion

- Synthetic Opioids

According to the Centers for Disease Control and Prevention, deaths from synthetic opioids increased by 79% between 2013 and 2014[1]. During that period submissions to the U.S. Drug Enforcement Administration saw a 426% increase in drug products testing positive for fentanyl. Fentanyl is a well characterized compound, but distinguishing between its isomeric forms such as valeryl fentanyl, parafluorofentanyl, and furanyl fentanyl can be problematic using traditional GC-MS methods.

Figure 1 shows a gas chromatography–vacuum ultraviolet spectroscopy (GC–VUV) chromatogram of synthetic opioids parafluorofentanyl, valeryl fentanyl, and furanyl fentanyl. Fentanyl was run separately, and its chromatogram is not shown due to the relative differences in concentration. When the VUV spectra of these isomers are overlaid, distinct differences are observed despite the similarities in chemical structure. Valeryl fentanyl varies only by the addition of two side chain carbon atoms and parafluorofentanyl by a fluorine atom attached to one of its benzene rings. The differences in spectral features are reproducible and provide distinguishing characteristics that allow positive identification through the VUV spectral library.

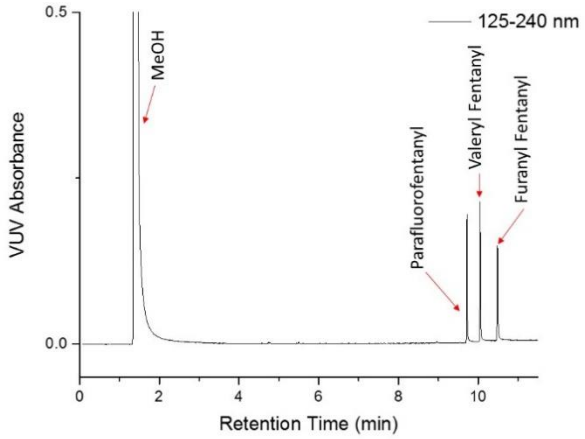

Figure 1: Gas chromatography–vacuum ultraviolet spectroscopy (GC–VUV) chromatogram of synthetic opioids parafluorofentanyl, valeryl fentanyl, and furanyl fentanyl.

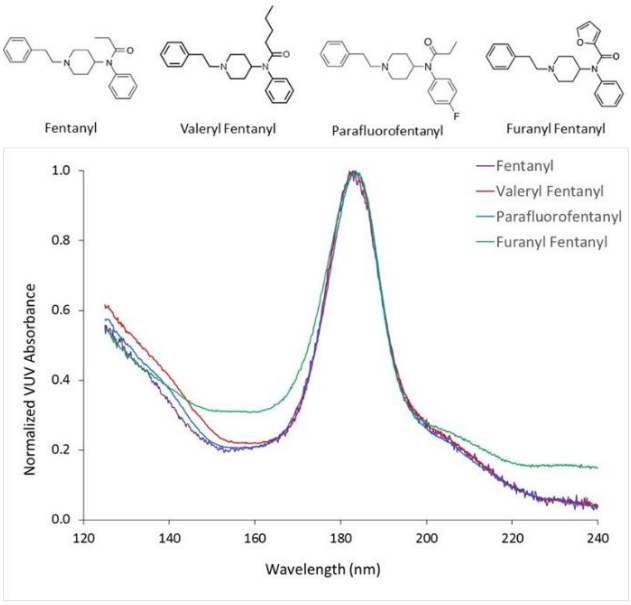

Figure 2: VUV spectral overlay of synthetic opioids fentanyl, parafluorofentanyl, valeryl fentanyl, and furanyl fentanyl.

➢ Amphetamines

Distinguishing between amphetamine isomers by GC-MS has been an ongoing problem for law enforcement agencies around the world. Many of the difficulties center on the fact that amphetamine mass spectra are rarely distinct, and their most abundant ions are typically low mass. These factors are evident when comparing the mass spectra[2] of phentermine and methamphetamine shown in figures 3 and 4. The most abundant ion of both compounds has a mass of 58, which is a less than ideal choice of quantitation ion. Additionally, using this as a precursor ion for MS/MS would prove difficult at best. The ion with mass of 91 is very common to alkylated aromatics and does not provide clear differentiation between isomers.

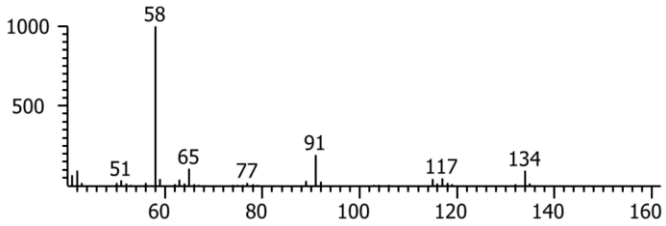

Figure 3: MS spectrum of phentermine

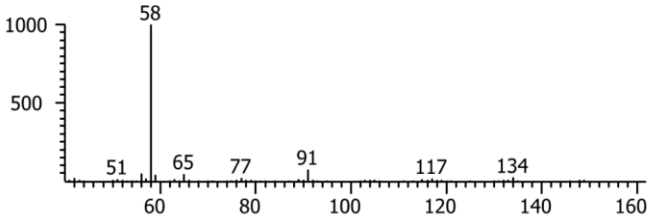

Figure 4: MS spectrum of methamphetamine

Figure 5 shows a GC–VUV chromatogram of amphetamines phentermine, methamphetamine, and pseudoephedrine along with the cathinone methcathinone. Representative spectra of each compound are shown adjacent to the corresponding chromatographic peaks to demonstrate the 3D nature of GC-VUV data. The VUV spectral overlay shows very distinct features and clear differentiation of the amphetamine isomers. The cathinone methcathinone was included in this analysis because it varies from methamphetamine by only a carbonyl group. Both compounds have significantly different spectral profiles despite their subtle variations.

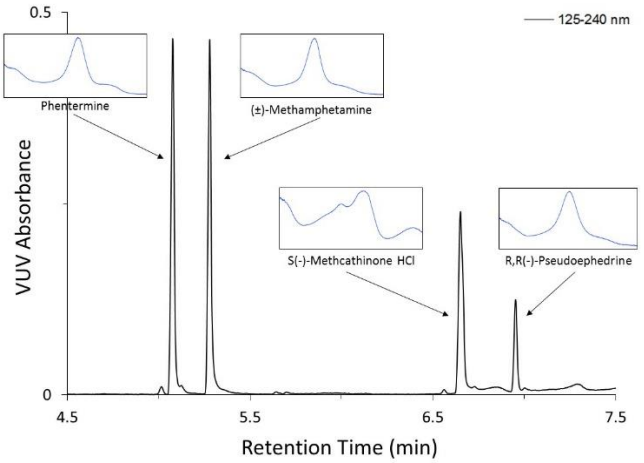

Figure 5: GC–VUV chromatogram of amphetamines phentermine, methamphetamine, and pseudoephedrine along with cathinone methcathinone. Representative spectra of each compound are shown adjacent to the corresponding chromatographic peaks to demonstrate the 3D nature of GC-VUV data.

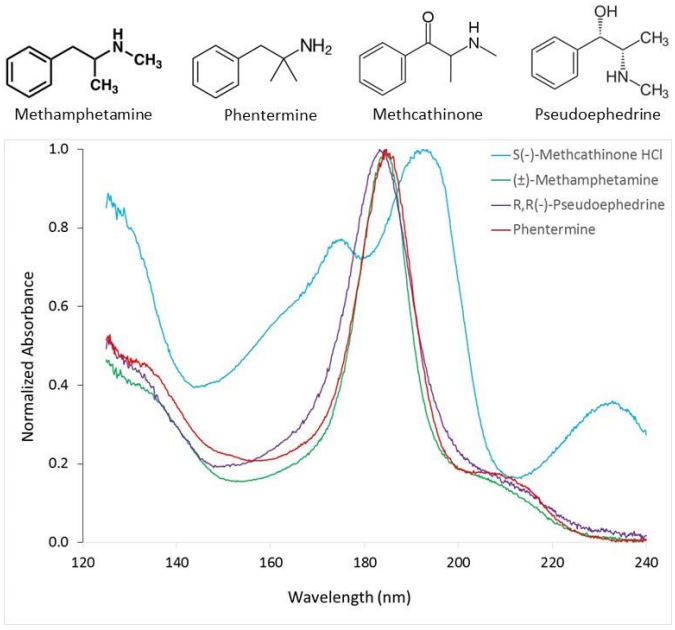

Figure 6: VUV spectral overlay comparison of amphetamine and cathinone standards. Subtle differences in spectra are sufficient to repeatably differentiate between structural isomers and enable their specific quantitation.

Figure 7 shows a GC–VUV chromatogram of amphetamines para-methoxyamphetamine, para-methoxymethamphetamine, and 3,4-MDMA. Their respective VUV spectra are compared in Figure 8. The spectra of para-methoxyamphetamine and para-methoxymethamphetamine are structurally similar but distinct enough for unambiguous identification through the VUV spectral library.

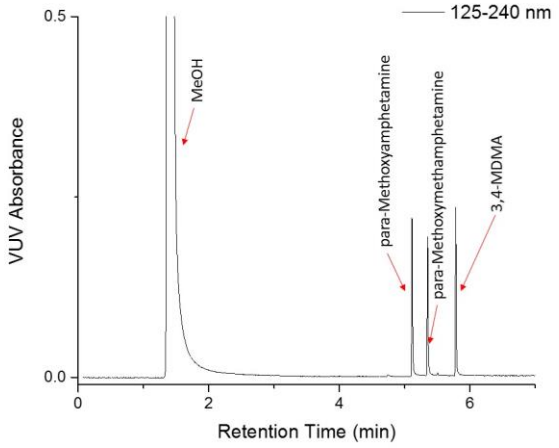

Figure 7: GC–VUV chromatogram of amphetamines para-methoxyamphetamine, para-methoxymethamphetamine, and 3,4-MDMA.

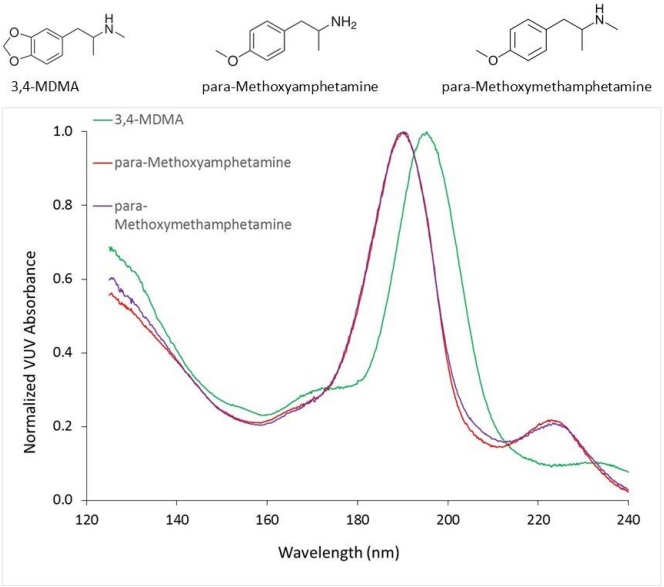

Figure 8: VUV spectral overlay of amphetamines para-methoxyamphetamine, para-methoxymethamphetamine, and 3,4-MDMA.

➢ Synthetic Cathinones

Synthetic cathinones, also known as "bath salts," were first brought to the attention of law enforcement in 2010 after reports to US poison centers[3]. These drugs have been made available online and in retail locations such as gas stations and "head shops." Because they are typically labeled as not being intended for human consumption, the compounds are difficult to regulate through drug prohibition laws.

Figure 9 is a GC-VUV chromatogram of cathinones ethcathinone, pentylone, 2-methyl-α-pyrrolidinopropiophenone, and 3,4-methylenedioxy pyrovalerone. The VUV spectral profiles of each of these compounds can be seen in Figure 10. The spectral similarities of the cathinone compound class are evident in this comparison. The VUV software can be automated to positively identify compounds by their classes even when specific analytes are not in the VUV spectral library. In this example, the identity of each cathinone was verified and quantitative values provided despite low starting concentrations.

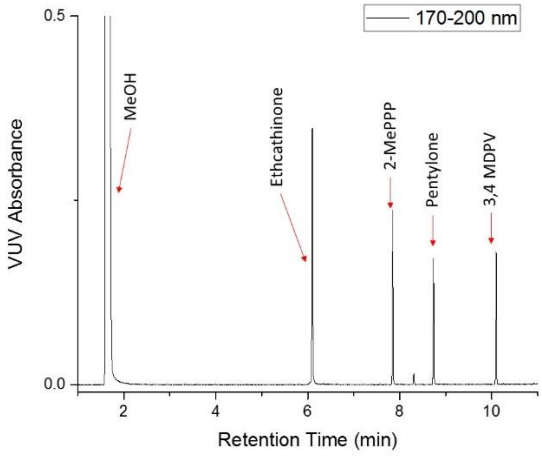

Figure 9: GC–VUV chromatogram of cathinones ethcathinone, 2-methyl-α-pyrrolidinopropiophenone (MePPP), pentylone, and 3,4-methylenedioxy pyrovalerone (MDPV).

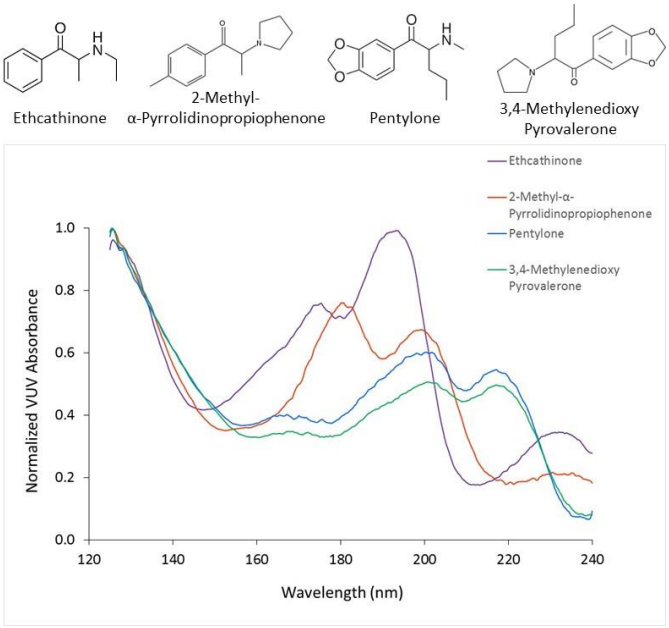

Figure 10: VUV spectral overlay of cathinones ethcathinone, 2-methyl-α-pyrrolidinopropiophenone, pentylone, and 3,4-methylenedioxy pyrovalerone.

➢ Benzodiazepines

Benzodiazepines, also known as tranquilizers, are drugs commonly prescribed for indications such as anxiety, insomnia, alcohol withdrawal, and seizure control. When used in combination with alcohol or opioids the effect is often fatal. Flubromazolam, etizolam, and clonazolam were analyzed by GC-VUV because of their chemical similarities. They vary mostly by substitutions of bromine, fluorine, chlorine, alkyl, and nitro groups at common structural locations. A chromatographic overlay of all three compounds run individually is shown in Figure 11. The distinctive spectral shape of the benzodiazepine compound class can be viewed in Figure 12. Each of the compounds analyzed displayed characteristic spectra that allowed for easy identification through by the VUV spectral library.

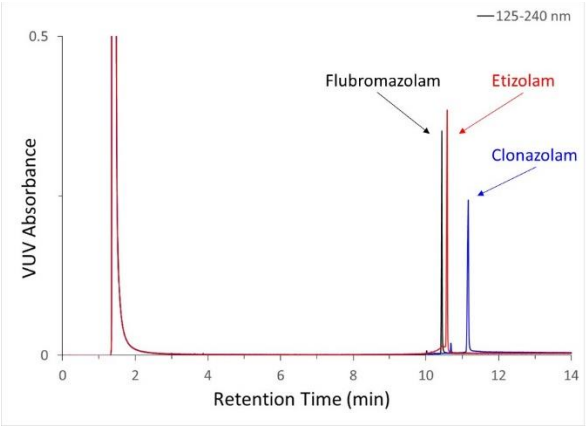

Figure 11: GC–VUV chromatographic overlay of benzodiazepines flubromazolam, etizolam, and clonazolam.

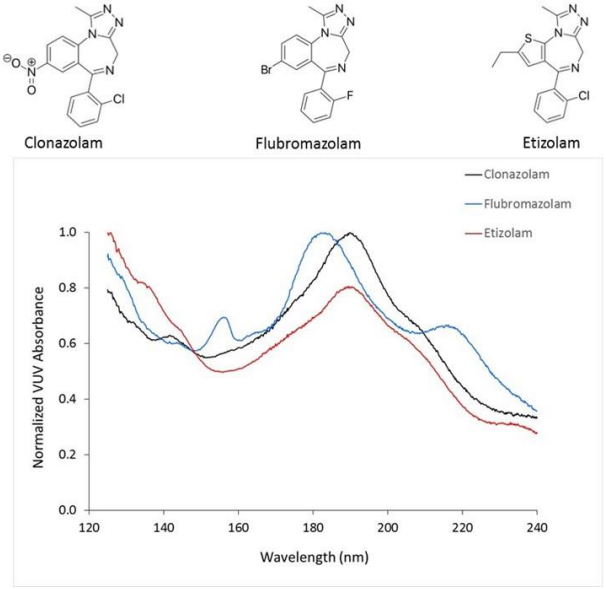

Figure 12: VUV spectral overlay of benzodiazepines flubromazolam, etizolam, and clonazolam.

- Synthetic Cannabinoids

The abuse of synthetic cannabinoids, also known as Spice or K2, is a growing problem across the U.S. Inert herbal blends sprayed with these synthetic cannabinoid compounds have led to numerous overdose deaths. Legal cannabis growers in the Pacific Northwest have also been caught spraying their harvests with these synthetic compounds to increase the perceived potency of their products.

THC analogues AB-FUBINACA (ABF), 2-ABF, 3-ABF, and 5-fluoro-CUMYL-PINACA were analyzed by GC-VUV. They belong to the indazole synthetic cannabinoid compound class and show similar but distinct VUV spectral features as shown in Figure 13.

Figure 14 shows a spectral comparison of the naturally occurring cannabinol with the synthetic cannabinoids AM2201 and 5-fluoro-CUMYL-PINACA. Cannabinol, AM2201, and 5-fluoro-CUMYL-PINACA represent the phytocannabinoid, indazole, and naphthoylindole chemical classes, respectively. It is clear that each compound class has distinct spectral characteristics, yet they share features common to all cannabinoids. Figure 15 demonstrates this point by highlighting the spectral features that are inherent to the phytocannabinoid and indazole compound classes.

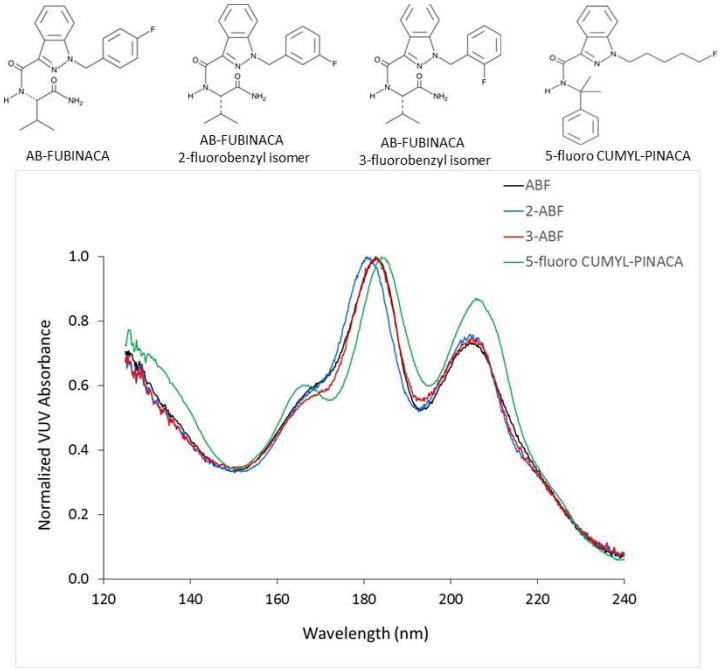

Figure 13: VUV spectral overlay of THC analogues AB-FUBINACA (ABF), 2-ABF, 3-ABF, and 5-fluoro-CUMYL-PINACA belonging to the indazole synthetic cannabinoid compound class.

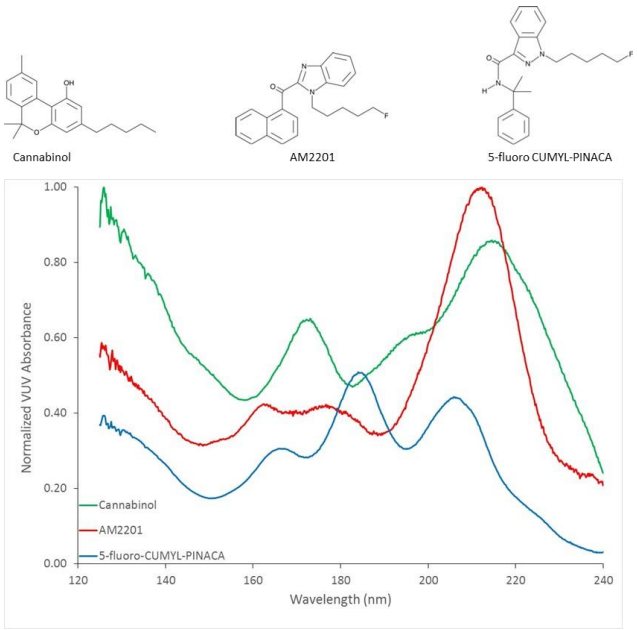

Figure 14: A VUV spectral overlay comparison of cannabinol, AM2201, and 5-fluoro-cumyl-pinaca which represent the phytocannabinoid, indazole, and naphthoylindole compound classes, respectively.

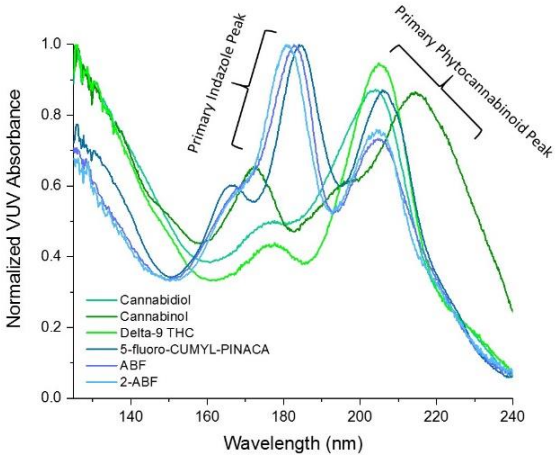

Figure 15: An overlay comparing VUV spectral features of phytocannabinoid and indazole compound classes.

Conclusion

GC-VUV presents the U.S. DEA and global regulatory agencies with a high throughput solution for the analysis of synthetic drugs of abuse. GC-VUV separations can typically be completed in less than 15 minutes. In addition, compound identification and automated spectral quantitation through VUV software require little time and effort. Further adding to the unique value of VUV spectroscopy is its unmatched selectivity of isoforms combined with the ability to characterize compounds by their classes. The VGA gas chromatography detector product line provides a powerful new tool that is capable of keeping up with the rapidly changing complexities of drug enforcement and regulation.

For more detailed information please visit our website at www.vuvanalytics.com, or contact us at info@vuvanalytics.com.

Acknowledgements

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Lindsey Shear-Laude and Alex Hodgson of VUV Analytics for the analysis of the drug standard samples.

References

1. A dramatic surge in fentanyl cases fuels opioid epidemic, Nadia Kounang, CNN, August 25, 2016.
2. Analysis of drug isomers using Gas Chromatography with Vacuum Ultraviolet Detection (GC–VUV), Da Vinci Laboratory Solutions, Nov 2015.
3. Spiller HA, Ryan ML, Weston RG, Jansen J (2011). "Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States". Clinical Toxicology. 49 (6): 499–505.

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