SAFETY AND SECURITY

TECH NOTE 3.0

Analysis of Fentanyl and Its Analogs with a Handheld API Mass Spectrometer and In-Source CID

Overview

Microscale ion trap mass spectrometers have been previously demonstrated operating at unusually high pressures in the range of 1 to 10 torr,[1] a pressure regime serviceable by simple scroll or piston pumps. A handheld version of this technology has been engineered with an atmospheric inlet to accommodate a dual-polarity atmospheric pressure ion source. The continuous flow inlet of the instrument (~6 sccm) supports continuous real-time vapor analysis, but the system can also be configured with a thermal desorber to facilitate the analysis of low-volatility materials of interest such as drugs and explosives.

The United States and numerous other countries have suffered from a startling rise in the abuse of opioids, and of particular concern, fentanyl and its analogs. Fentanyls can be purchased in large quantities on the dark web, and owing to their extreme potency and economics, their inclusion in street drugs or counterfeit analgesics is unfortunately inevitable. Their extreme potency poses a lethal threat not only to unsuspecting users of contraband, but also the first responders that attend to overdose and interdiction activities, and the possibility of even more extreme scenarios of mass incapacitation/death has been documented.[2]

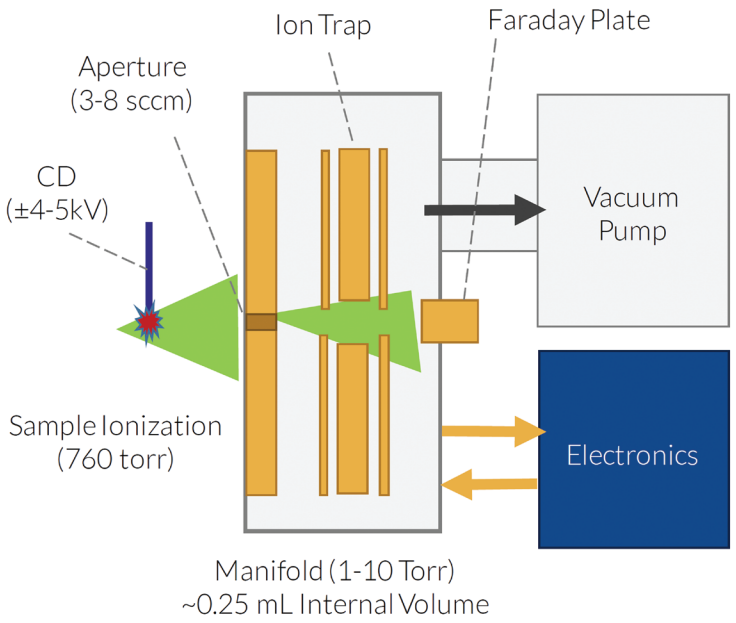
In this work we report on the results of optimization of an in-source CID sequence and subsequent characterization of the handheld API mass spectrometer/algorithm performance for the analysis of both neat and heavily cut samples containing various fentanyl analogs.

1. An in-source CID sequence was found to provide successive and selective fragmentation across fentanyl analogs and other opioids with low nanogram sensitivity
2. The in-source CID and atmospheric ionization seem to provide very strong selectivity in the presence of substantial cutting agent/diluent
3. The multi-step dissociation / neutral loss mechanism has proven predictive of otherwise unknown fentanyl analogs.

ITMS & API

The system employs a stretched-length ion trap[3,4] with < 250 um r0 operating at multiple radial frequencies around 10 MHz. A small multistage scroll pump of 908 Devices' design services a 3-8 sccm continuous inlet flow at 1-10 torr of operating pressure in the trap, minimizing overall system SWaP. The system employs an extremely high gain microfabricated transimpedance amplifier that supports high pressure operation for ion detection.

A dual polarity corona discharge ionizer provides highly efficient generation of both positive and negative ions without a dopant. These ions enter the MS through an orifice aperture capable of supporting voltages up to 180 V.



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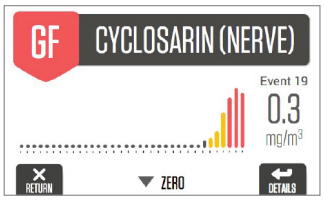
Current Target Coverage



Fentanyls In Current MX908 Drug Library:

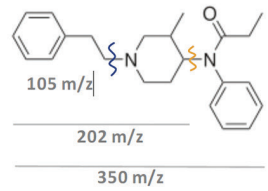
fentanyl	3-methylfentanyl
acetylfentanyl	butyrylfentanyl
sufentanil	furanylfentanyl
remifentanil	alfentanyl
carfentanil	benzylfentanyl

CID of Opioids

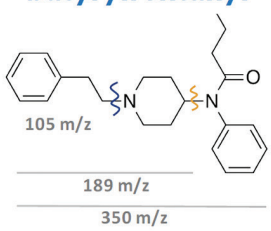
When configured for drug analysis, the system automatically runs full mass spectral scans several times a second at 3 different CID energy levels. Like in all systems, the scan speed must be balanced to provide sufficient sensitivity while also balancing resolving power both in the mass domain and time domain (during the thermal desorption).

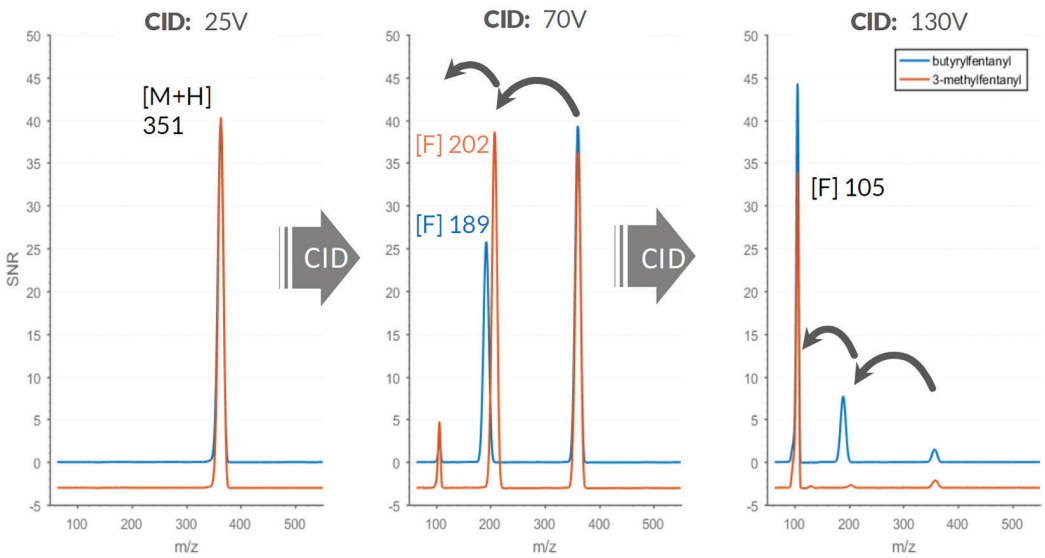
Two Isobaric Fentanyl Analogs

3-methylfentanyl



butyrylfentanyl





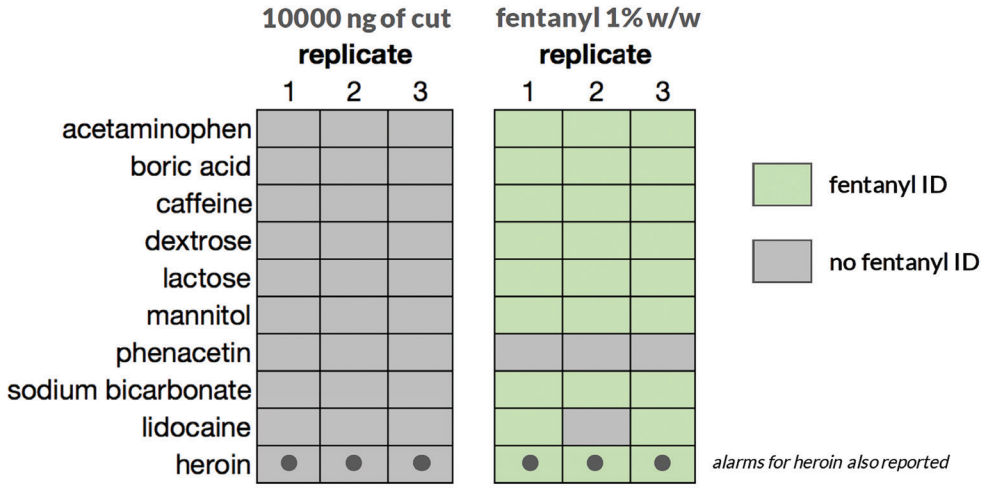
Limits of Detection

Standards were procured from Cayman Chemical of various fentanyl analogs in methanol at 1 mg/mL concentrations. Aliquots of the standards were dropcast onto the MX908 thermal desorption swabs and subsequently analyzed using the MX908 in its standard "Trace Mode" (thermal desorption MS) as well as the thermal desorption mode with fentanyl-optimized in-source CID ("CID Mode"). Doses were reduced by 50% until less than 90% probability of detection was observed over replicate doses at 90% confidence. Blanks were run between each assay to verify cleanliness. Ephedrine was used as an initial comparator in a 5 device study, with carfentanil and remifentanil subsequently run for detailed LOD's on two of the five devices. All dosing, analyses, and results were run/reported by independent government test personnel.

	Estimated LOD: lowest Pr(D) > 90% at 90% confidence				
UNIT	ephedrine (Trace Mode ng)	carfentanil (Trace Mode ng)	carfentanil (CID Mode ng)	remifentanil (Trace Mode ng)	remifentanil (CID Mode ng)
MX908 A	3.1	n/a	n/a	n/a	n/a
MX908 B	37.6	62.5	15	25	25
MX908 C	35.8	n/a	n/a	n/a	n/a
MX908 D	34.5	62.5	15	25	25
MX908 E	7.2	n/a	n/a	n/a	n/a

Detection with Cut Materials

Dilute solutions of various cutting agent were prepared in MeOH. As above, solutions of cutting agent, and then cutting agent plus drug were dropcast and analyzed in the MX908's Drug Hunter mode employing CID.



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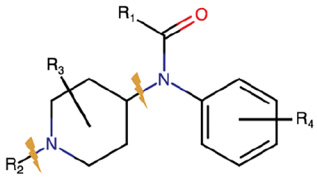
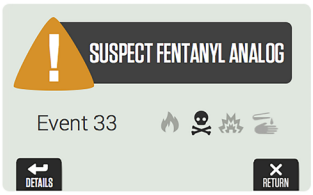
Detection of Novel Analogues of Fentanyl



Expected Ions (⚡):
Standard MS: $[M+H]^+$
mid V: $[R_2+R_3+C_5NH_9]^+$
high V: $[R_2+H]^+$

Current search space:
R_1 = 13 possible substituent groups
R_2 = 8 possible substituent groups
R_3 = 5 possible substituent groups
R_4 = 5 possible substituent groups



Fentanyl Template:
The broader class of analogs of fentanyl can be described by the template at left. There are >3000 potential analogs including isomers.

Detection/Identification:
The algorithms evaluate multivariate log-likelihoods for the probability of each of the candidate analogs given the observed [M+H]+, and mass spectral dissociation and loss patterns. Measurements with sufficient log-likelihoods are returned as possible suspect analogs to the operator.

Performance:
Ten different fentanyl analogs are already contained in the MX908 Drug Library, but we eliminated them from the library to test the efficacy of the algorithmic analog detection scheme. FPR was evaluated across a number of environmental and powder samples known not to contain fentanyl.

		truth: fentanyl analog	truth: clear	
prediction	suspect fentanyl	71	9	80
prediction	clear	51	326	377
		122	335	457

positive predictive value: 95%
negative predictive value: 70%
PPV/NPV @ 50% population prevalence

sensitivity: 59%
specificity: 97%

Conclusions

In today's evolving threat landscape, handheld mass spectrometry offers great versatility to crosscut multiple missions from CWA detection/identification to the analysis of opioids including fentanyls. Thermal desorption of fentanyl-containing samples with heavy contamination demonstrated stronger performance than can be achieved with common field optical systems (e.g. Raman and FTIR). Detection limits in the sub-100 ng range are practical with very high selectivity. The in-source CID approach demonstrated also appears to offer a major advance in the detection of previously unknown analogs of fentanyl.

References:
1. K. H. Blakeman et al., *High Pressure Mass Spectrometry: The Generation of Mass Spectra at Operating Pressures Exceeding 1 Torr in a Microscale Cylindrical Ion Trap*, Anal. Chem. 88(10) 2016: 5378-5384 **2.** J.R. Riches et al., *Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentaniland remifentanil use*, J. Anal. Tox. 36 2012: 647-656 **3.** J. M Ramsey & K.P. Schultze US PTO 8,878,127 **4.** J. M Ramsey & K.P. Schultze *Characterization of a Novel Ion Trap Geometry for Higher Capacity Trapping in Microscale Mass Spectrometry* ASMS 2014

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