

Application Note AN-RA-007

Enhancement of Raman intensity for the detection of fentanyl

Easy EC-SERS protocol for the screening of fentanyl with screen-printed electrodes

Fentanyl is a potent synthetic opioid drug used as an analgesic and anesthetic. It is approximately 100 times more potent than morphine and 50 times more potent than heroin. However, illicit fentanyl is distributed and sold illegally around the world on the black market. A fentanyl overdose may result in stupor, changes in pupil size, cold and clammy skin, cyanosis, coma, and respiratory failure leading to death. Two milligrams of fentanyl can be lethal depending on body size, tolerance, and past usage.

Identification and detection are imperative because fentanyl-related overdoses have rapidly become a major public health crisis in many communities in countries such as the USA and Canada.

The development of new methods based on the combination of electrochemical surface-enhanced Raman spectroscopy (EC-SERS) and screen-printed electrodes (SPEs) provides a rapid, efficient, and accurate approach for the detection of fentanyl [1].

INSTRUMENTATION AND SOFTWARE

Measurements in this study were performed using a SPELEC RAMAN instrument (785 nm laser), a Raman probe corresponding to the laser wavelength, and a Raman spectroelectrochemical cell for screen-printed electrodes (Figure 1).

Gold and silver SPEs (220BT and C013, respectively) were used due to their EC-SERS features.

The SPELEC RAMAN instrument was controlled with DropView SPELEC, a dedicated spectroelectrochemical software that simultaneously acquires electrochemical and optical information. All hardware and software used for this study is compiled in Table 1.



Figure 1. SPELEC RAMAN instrument and Raman probe used in combination with a Raman spectroelectrochemical cell for screen-printed electrodes.

Table 1. Hardware and software equipment overview.

Equipment	Article number
Instrument	SPELECRAMAN
Probe	RAMANPROBE
Raman spectroelectrochemical cell for SPEs	RAMANCELL
Gold SPE	220BT
Silver SPE	C013
Connection cable for SPEs	CAST
Software	DropView SPELEC

RESULTS: CHARACTERIZATION AND DETECTION OF FENTANYL

Detection of fentanyl (Figure 2) was performed by the electrochemical activation of metallic SPEs concurrently with the drug's presence in solution. The protocol consists of two steps in a single experiment: (1) the electrochemical generation of metallic nanostructures with SERS properties and (2) detection of fentanyl present in the solution.

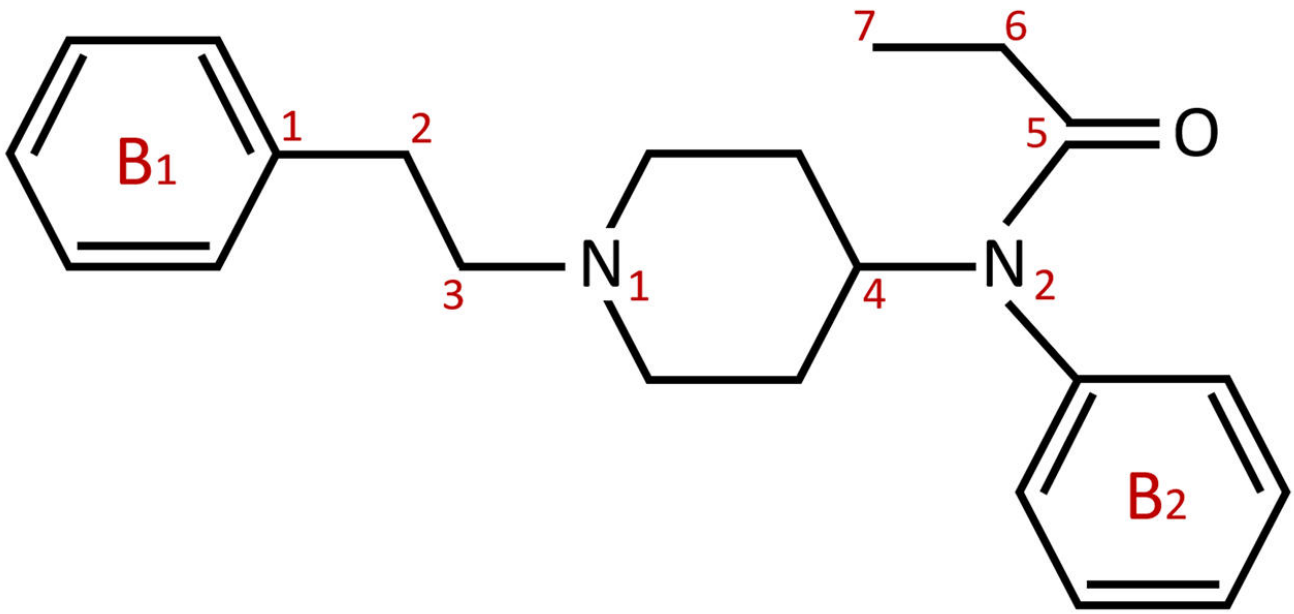


Figure 2. Chemical structure of fentanyl. The number assignments correspond to the vibrational assignment of SERS bands in Table 2.

Two SPEs were evaluated—gold (220BT) and silver (C013)—due to the enhancement of Raman intensity associated with these electrodes.

Detection of fentanyl with 220BT was performed in 1 × 10^{-5} mol/L fentanyl and 0.1 mol/L KCl by cyclic voltammetry, scanning the potential from +0.70 V to +1.40 V and back to -0.20 V, with a scan rate of 0.05 V/s (Figure 3a).

Experiments with C013 were carried out in 1 × 10^{-5} mol/L fentanyl, 0.1 mol/L $HClO_4$, and 0.01 mol/L KCl. The potential was scanned from 0.00 V to +0.40 V and back to -0.40 V, with a scan rate of 0.05 V/s (Figure 3b).

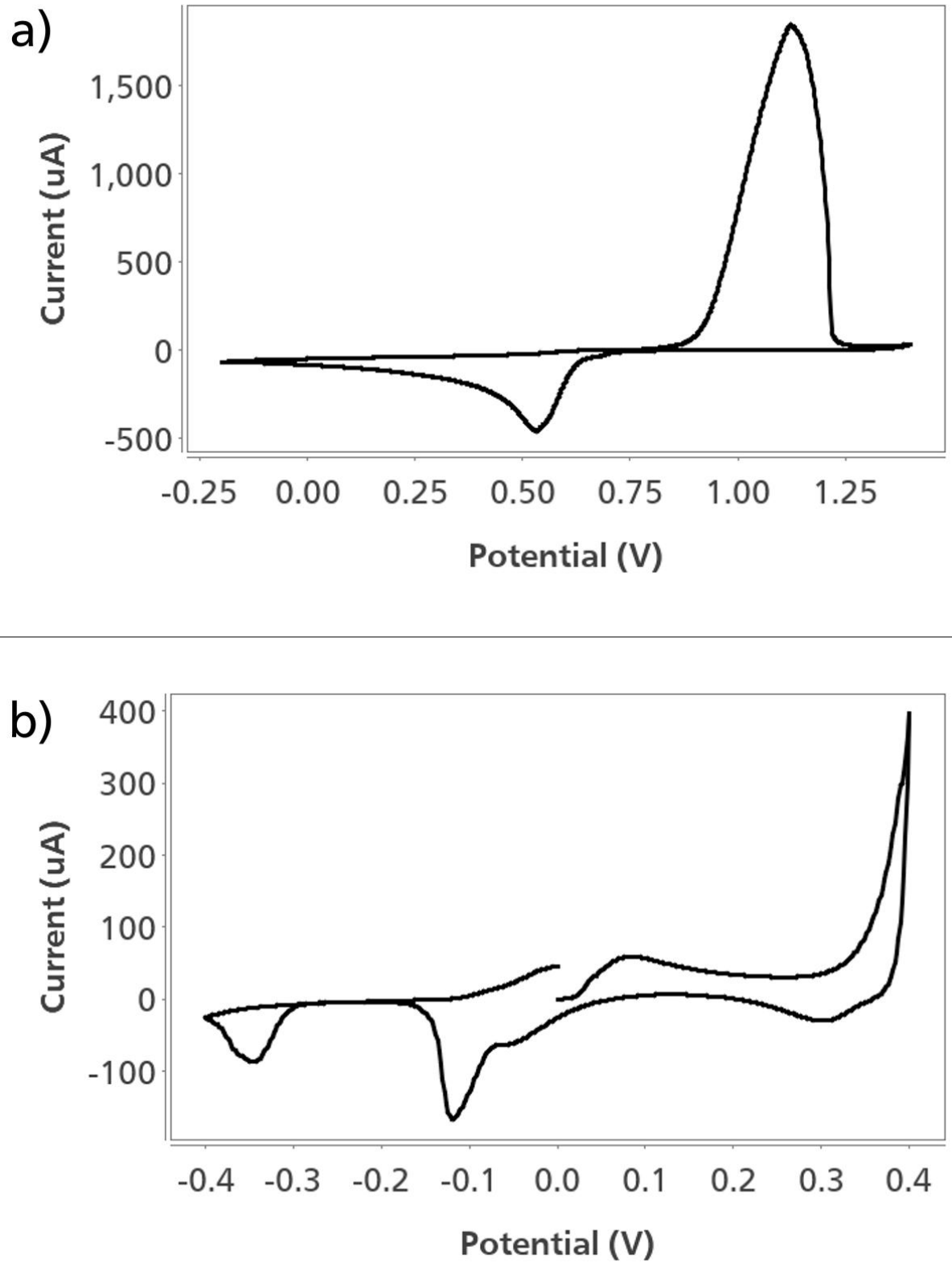


Figure 3. Cyclic voltammograms obtained with a) 220BT in 0.00001 mol/L fentanyl and 0.1 mol/L potassium chloride, and b) C013 in 0.00001 mol/L fentanyl, 0.1 mol/L perchloric acid, and 0.01 mol/L potassium chloride.

Spectroelectrochemical detection with both SPEs is based on the same methodology: the initial oxidation of the metallic surface followed by its reduction to generate Au or Ag nanoparticles (NPs) with a SERS effect. Although the characteristic Raman bands of fentanyl are detected once these nanostructures are generated, the highest Raman intensity was obtained during the final part of the experiment (+0.50 V, anodic scan) with 220BT, and at -0.40 V when working with C013.

Figure 4 displays the characteristic spectrum of fentanyl obtained with Au and Ag SPEs. Different bands are detected, with the most intense and representative band located at 1000 cm^{-1}.

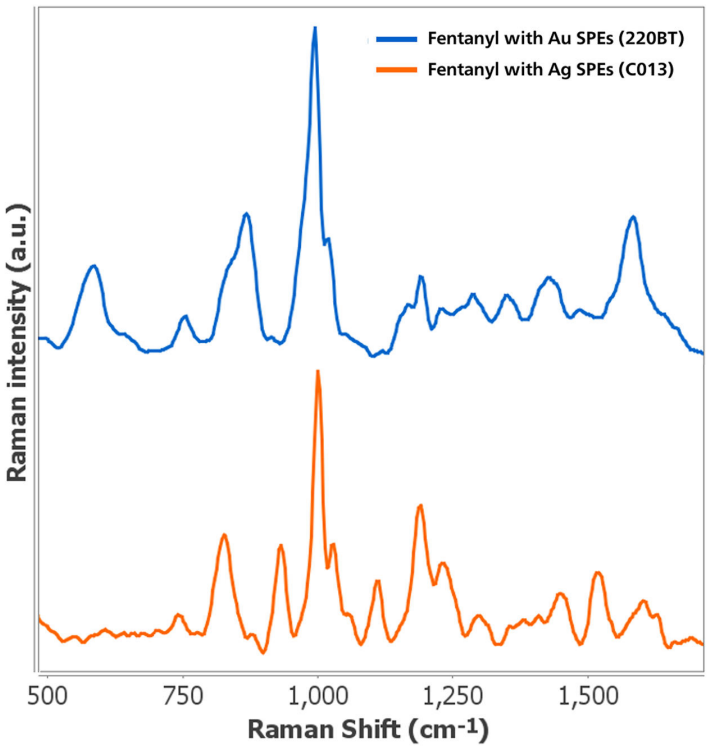


Figure 4. SERS spectrum of 0.00001 mol/L fentanyl obtained with 220BT (blue line) and C013 (orange line) SPEs.

Table 2 summarizes the assignment of the observed Raman bands with the characteristic vibrational modes of fentanyl. The interaction of fentanyl with Au and Ag SERS substrates is not identical; some vibrational modes are only detected with one metal, and the shifting of several bands is also observed.

Table 2. Vibrational assignment of SERS bands of fentanyl obtained with Au (220BT) and Ag (C013) SPEs [2,3] (ν: stretching; δ: in-plane bending; ρ: rocking; γ: out-of-plane bending; τ: twisting; ω: wagging; β: ring breathing).

SERS band (cm^{-1})		Assignment
Au	Ag	
588	-	$\delta\ (ring)_{B1,B2}$, $\rho\ (CH_2)_{alkyl}$, $\rho\ (CH_3)$
758	741	$\tau\ (CH_3)$, $\rho\ (CH_2)_{pip}$, $\delta\ (C_5\text{-}C_6\text{-}C_7)$
873	826	$\nu\ (C_1\text{-}C_2\text{-}C_3\text{-}N_1)$, $\beta\ (ring)_{B1}$
-	932	$\gamma\ (CH)_{B2}$
1000	1000	$\delta\ (CC)_{B2}$, $\nu\ (C_5\text{-}C_6\text{-}C_7)$
1026	1029	$\nu\ (CC)_{B1,B2}$, $\delta\ (CH)_{B1,B2}$
-	1112	$\nu\ (CC)_{B2}$
1174	-	$\delta\ (CH)_{B1,B2}$
1202	1190	$\nu\ (N_1\text{-}C_3\text{-}C_2\text{-}C_1)$; $\tau\ (CH_2)_{C2}$
1236	1239	$\nu\ (C_4\text{-}N_2)$, $\omega\ (C_6\text{-}C_7\text{-}H)$
1296	1303	$\tau\ (C_3\text{-}H)$
1359	1354	$\omega\ (CH)_{pip}$, $\tau\ (CH)_{pip}$
1439	1444	$\delta\ (H\text{-}C\text{-}N_2)$
1598	1601	$\nu\ (CC)_{B1}$
-	1629	$\nu\ (CC)_{B1}$

In order to demonstrate the usefulness of this method, the intensity of Raman band at 1000 cm^{-1} obtained with 220BT was analyzed with varying fentanyl concentrations. The calibration curve in Figure 5 shows linear behavior of the Raman intensity from 1×10^{-6} mol/L (0.33 µg/mL) to 1×10^{-5} mol/L (3.37 µg/mL) fentanyl. The high correlation coefficient value (R^2 = 0.997) ensures the suitability and the sensitivity of this EC-SERS method for the detection of fentanyl in the mentioned concentration range.

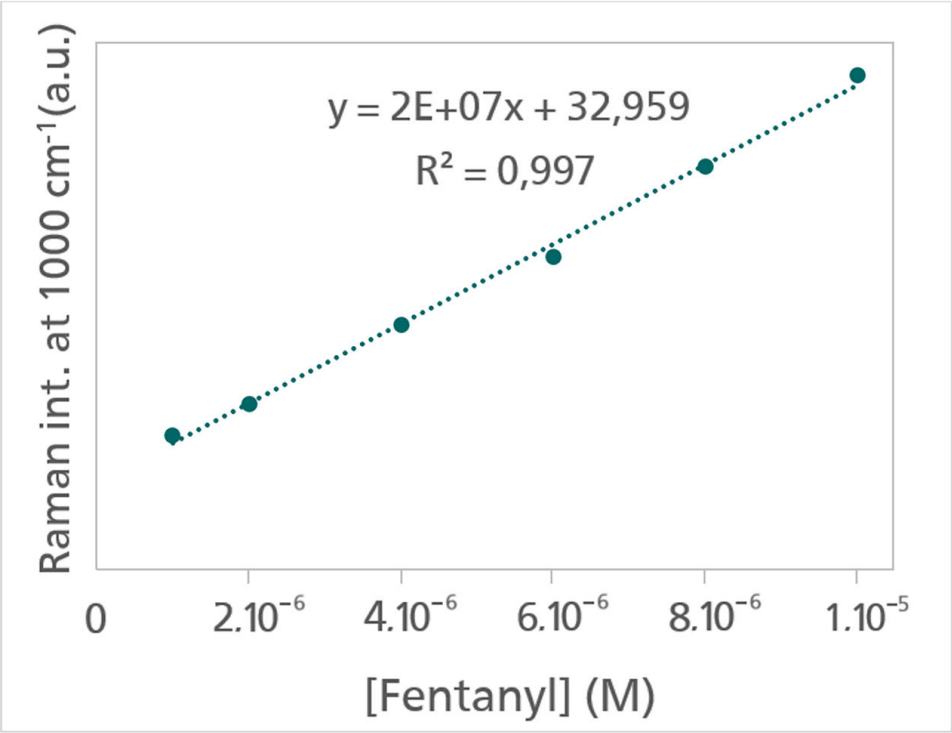


Figure 5. Calibration plot of Raman intensity at a specific wavelength with different concentrations of fentanyl in 0.1 mol/L KCl using 220BT.

CONCLUSION

The development of a sensitive fentanyl detection method based on the SERS effect is achieved. Au and Ag SPEs provide interesting results which are not only useful in the characterization of fentanyl, but also for other analytical purposes. The electrochemical activation of 220BT and C013 SPEs along with the detection of fentanyl in a single experiment represents a rapid and easy procedure that facilitates the spectroelectrochemical measurements. The calibration curve obtained with 220BT exhibits linear behavior from 1×10^{-6} mol/L (0.33 µg/mL) to 1×10^{-5} mol/L (3.37 µg/mL) fentanyl, demonstrating the wide potential of this method.

REFERENCES

1. Ott, C. E.; Perez-Estebanez, M.; Hernandez, S.; et al. Forensic Identification of Fentanyl and Its Analogs by Electrochemical-Surface Enhanced Raman Spectroscopy (EC-SERS) for the Screening of Seized Drugs of Abuse. *Frontiers in Analytical Science* **2022**, *2*. https://doi.org/10.3389/frans.2022.834820.
2. Wang, L.; Deriu, C.; Wu, W.; et al. Surface Enhanced Raman Spectroscopy, Raman, and Density Functional Theoretical Analyses of Fentanyl and Six Analogs. *Journal of Raman Spectroscopy* **2019**, *50* (10), 1405–1415. https://doi.org/10.1002/jrs.5656.
3. Leonard, J.; Haddad, A.; Green, O.; et al. SERS, Raman, and DFT Analyses of Fentanyl and Carfentanil: Toward Detection of Trace Samples. *Journal of Raman Spectroscopy* **2017**, *48* (10), 1323–1329. https://doi.org/10.1002/jrs.5220.

RELATED APPLICATION NOTES

AN-RA-006 New strategies for obtaining the SERS effect in organic solvents

AN-SEC-001 Spectroelectrochemistry: an autovalidated analytical technique – Confirm results via two different routes in a single experiment

AN-SEC-002 Gathering information from spectroelectrochemical experiments – Calculation of electrochemical parameters from data

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CONFIGURATION



Raman Probe

Reflection probe designed to be used with a single excitation 785 nm wavelength (up to 500 mW). Suitable to work with DropSens Raman Cell for Screen-Printed Electrodes or with any conventional Raman set-up.



Raman Cell for Screen-Printed Electrodes

Black teflon reflection cell for performing Raman Spectroelectrochemistry with screen-printed electrodes in combination with ref. RAMANPROBE.



Screen-Printed Gold Electrode (Aux.:Au; Ref.:Ag) / Ink BT

Screen-Printed Gold Electrode (Aux.:Au; Ref.:Ag) / Ink BT. Suitable for working with microvolumes, for decentralized assays or to develop specific sensors.



Screen-Printed Silver Electrode (Aux.:C; Ref.:Ag)

Screen-Printed Silver Electrode (Aux.:C; Ref.:Ag). Working Electrode of 1.6 mm diameter.



Stat Cable connector for Screen-Printed Electrodes

Connects any DropSens equipment with DropSens Screen-Printed Electrodes



Spectroelectrochemical Raman instrument (785 nm laser)

SPELECRAMAN is an instrument for performing spectroelectrochemical Raman measurements. It combines in only one box a laser class 3B (785 nm ± 0.5), a bipotentiostat/galvanostat and a spectrometer (wavelength range 787 – 1027 nm and Raman shift 35 - 3000 cm^{-1}) and includes a dedicated spectroelectrochemical software that allows optical and electrochemical experiments synchronization.