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Ionic Liquid-Modified Disposable Electrochemical Sensor Strip for Analysis of Fentanyl

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Ⓢ *Supporting Information*

ABSTRACT: The increasing prevalence of fentanyl and its analogues as contaminating materials in illicit drug products presents a major hazard to first responder and law enforcement communities. Electrochemical techniques have the potential to provide critical information to these personnel via rapid, facile field detection of these materials. Here we demonstrate the use of cyclic square wave voltammetry (CSWV) with screen-printed carbon electrodes (SPCE), modified with the room temperature ionic liquid (RTIL) 1-butyl-1-methylpyrrolidinium bis-(trifluoromethylsulfonyl)imide $[C_4C_1pyrr][NTf_2]$, toward such rapid "on-the-spot" fentanyl detection. This CSWV-based disposable sensor strip system provides an information-rich electrochemical fingerprint of fentanyl, composed of an initial oxidation event at +0.556 V (vs Ag/AgCl) and a reversible reduction and oxidation reaction at −0.235 and −0.227 V, respectively. The combined current and potential characteristics of these anodic and cathodic fentanyl peaks, generated using two CSWV cycles, thus lead to a distinct electrochemical signature. This CSWV profile facilitates rapid (1 min) identification of the target opioid at micromolar concentrations in the presence of other cutting agents commonly found in illicit drug formulations. The new protocol thus holds considerable promise for rapid decentralized fentanyl detection at the "point of need".
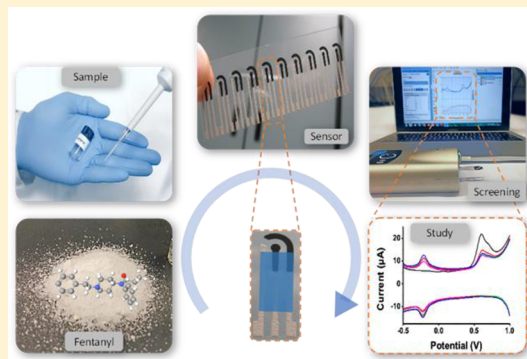
1. INTRODUCTION

Fentanyl is a potent synthetic opioid developed for use in acute analgesia and chronic pain management and is increasingly found in illicit drugs and counterfeit prescription pain medications.[1,2] The hidden presence of fentanyl analogues in street samples of illicit drugs is frequently associated with deaths, as a result of unintentional overdoses, and is the focus of a significant public health issue worldwide.[3−5] The dangers of exposure to fentanyl analogues in aerosol form were publicly demonstrated when they were used to subdue a hostage situation in Moscow in 2002, resulting in 125 fatalities.[6] While this incident remains a unique occurrence, the increasing occurrences of fentanyl within drug abuse situations mean that there is a substantial concern that law enforcers and first responders may be harmed by direct contact with these substances. The development of portable analytical technologies for fentanyl detection is therefore highly desirable to provide valuable and timely information to these front-line personnel field settings. Despite of these widespread attention and urgent needs, limited efforts have been devoted to the development of effective field screening tools for rapid low-cost detection of fentanyl.

Most of the methods for detecting fentanyl citrate are either time-consuming or required complex or expensive instrumentation. Gold standard methods for analyzing samples for fentanyl contamination are mass spectrometry based, which are limited to use in a laboratory setting.[7,8] More portable rapid, screening technologies include ion mobility spectroscopy, which offers rapid, sensitive fentanyl detection but can be confounded by complex mixtures commonly encountered in-the-field.[9−11] Thermal desorption direct analysis in real-time mass spectrometry demonstrates greater resilience to mixtures but is not yet fully portable and thus currently limited to use in mobile laboratories, emergency vehicles, and hospitals.[11] Commercial hand-held systems are available for Raman spectroscopy (TrueNarc) and spatially offset Raman spectroscopy (Agilent Resolve) for drug analysis in-field. However, the
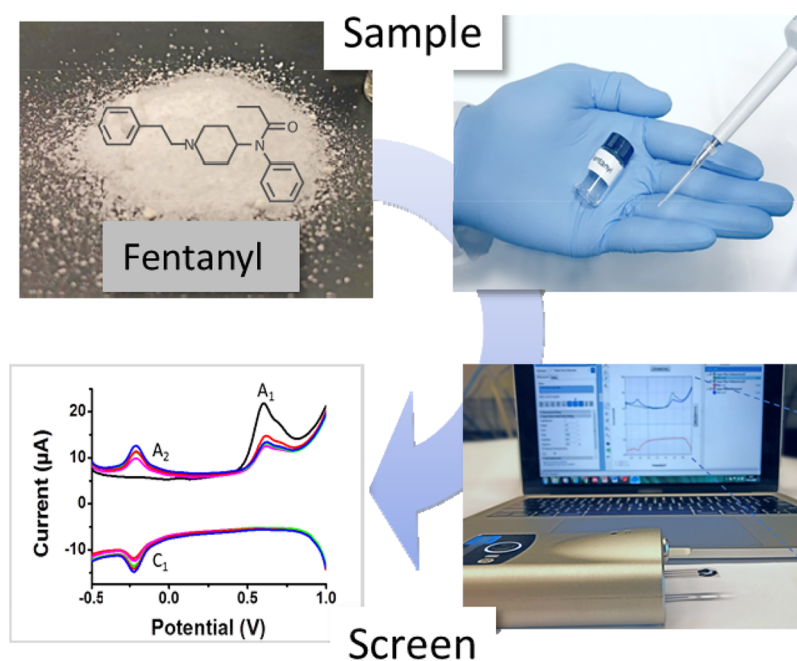
Figure 1. Concept overview for on-site fentanyl screening using SPCE, showing the solubilization of an unknown sample followed by direct electrochemical detection using a portable electroanalyzer and validation by the resulting distinct CSWV electrochemical fingerprint. **Safety note**: Owing to its extreme toxicity, fentanyl powder was not used here.

quality of the response from these instruments is dependent on the availability of spectral reference libraries and potential interferent background responses from sampled surfaces or cutting agents.[12] Surface enhanced Raman spectroscopy has also been used to detect fentanyl analogues, but it is currently limited by the bulky optical centralized instrumentation.[14,15] Immunoassays, particularly in the form of portable lateral flow tests, have attractive qualities for detection of fentanyl in the field.[13–15] However, the diverse structural nature of fentanyl analogues and the specificity of antibody reagents mean that individual assays are frequently unable to adequately detect all materials of interest.[13,14]

Electrochemical techniques have been widely demonstrated for field screening for a variety of analytes and offer a combination of fast response time and high sensitivity along with portable low-cost instrumentation.[16–19] Electrochemical devices are therefore extremely attractive for decentralized detection as tools to provide rapid chemical information to assist with incident management. Yet, to date, only a single example of applying an electrochemical technique, differential pulse voltammetry (DPV), to the fentanyl analogue sufentanil has been demonstrated.[20] It is thus essential to investigate more detailed applications of electrochemical systems for field detection of fentanyl.

In this work, we demonstrate how screen-printed carbon electrodes (SPCE) modified with the RTIL 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide $[C_4C_1pyrr][NTf_2]$ could serve as effective single-use disposable platforms toward in-field fentanyl screening applications in connection to a cyclic square wave voltammetry (CSWV) operation. Information-rich CSWV, where oxidative and reductive square-wave voltammetric scans are combined and presented in a cyclic manner, has been shown recently to be extremely attractive for providing distinct electrochemical fingerprints of complex mixtures such as propellant constituents of gunshot residues[19] and nitro-containing explosives.[21]

This technique is used here to offer a distinct electrochemical fingerprint for fentanyl, along with high speed and effective discrimination against the charging background current in connection to a disposable electrode strip. The new CSWV fentanyl detection-strip protocol is based on an initial irreversible oxidation reaction of the drug in the first anodic scan, which produces a reaction product that has reversible redox characteristics in subsequent cathodic and anodic scans. This distinct redox signature, combining the characteristics of the anodic and cathodic fentanyl signals from a minimum of two CSWV cycles (three individual SWV scans), including the peak ratios and separations, can facilitate rapid (1 min) identification of the target opioid drug in the presence of other potential cutting agents. Such unique coupling of information-rich sensitive voltammetry fingerprints with low-cost strip electrodes paves the way for effective and rapid decentralized sensing of fentanyl.

2. EXPERIMENTAL SECTION

2.1. Materials. Carbon ink (SunChemical, C2030519P4, Gwent electronic materials Ltd., UK) and Ag/AgCl ink (E2414, Ercon, Inc., MA) were used as received. Polyethylene terephthalate was used as a substrate for screen-printed electrodes. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received. Fentanyl (supplied in methanol) was diluted to 500 μM in phosphate buffer (0.1 M, pH 7.4) prior to use. Norfentanyl was reconstituted to 1 mg mL^{-1} in methanol (ultrapure, 99.8%) then diluted to 500 μM in phosphate buffer (0.1 M, pH 7.4) prior to use.

2.2. Synthesis of 1-Butyl-1-methylpyrrolidinium bis-(trifluoromethylsulfonyl)imide, $[C_4C_1pyrr][NTf_2]$. Synthesis of 1-butyl-1-methylpyrrolidinium chloride and subsequent synthesis of $[C_4C_1pyrr][NTf_2]$ were undertaken according to Rani and co-workers.[22] The resulting ionic liquid was washed twice with hexane and treated with activated charcoal to remove impurities. The charcoal was removed using filter

paper, followed by 0.2 μm PTFE filters to ensure complete removal of any particulates.

2.3. Preparation of Ionic Liquid Modified Screen-Printed Carbon Electrodes. Carbon ink was used to print both working and counter electrodes. Ag/AgCl was used as the reference electrode. Screen printing of electrodes was performed according to previous work.[23] The ionic liquid was diluted to 0.1% (v/v) in methanol, and 1 μL of the solution drop cast onto the working electrode. Each electrode was allowed to air-dry for 10 min prior to use.

2.4. Electrochemical Analysis of Fentanyl and Fentanyl Metabolites. All electrochemical measurements were performed using a PalmSens EmStat3 potentiostat controlled by PSTrace software (version 5.5) (Figure 1). The electrolyte used throughout was phosphate buffer (0.1 M, pH 7.4). Cyclic voltammetry (CV) was undertaken in 100 μL of electrolyte covering the three-electrode system using an E-step of 0.005 V and scan rate of 50 mV s^{-1}. The CSWV parameters were optimized at amplitude 0.05 V, E-step 0.004 V, and frequency of 25 Hz, respectively.

Safety note: Fentanyl is a powerful synthetic pharmaceutical product. Accidental exposure to even small quantities of fentanyl in powder or liquid form can lead to incapacitation and even death. To minimize the hazard from this material, minimal volumes of stock solution were generated for each experiment. Fentanyl was handled in this study only in solution to prevent extreme hazards from aerosolized powders. In addition, extreme caution was taken to prevent aerosolization of fentanyl solutions. All solutions containing fentanyl (including diluted stock solutions) were prepared and handled in a fume hood with continuous air flow. Complete skin protection for researchers was achieved using nitrile gloves, appropriate safety goggles, and users were further equipped with a half face respirator with high-efficiency particulate air (HEPA) filters.

3. RESULTS AND DISCUSSION

3.1. Electrochemistry of Fentanyl. This work aims to demonstrate the utility of electrochemical assay toward rapid on-site detection and identification of fentanyl. SPCE were chosen for this work due to their low cost mass production, which makes them extremely attractive as disposable field sensors (Figure 1). Besides its quantitative aspects, CSWV is used to provide distinct electrochemical signatures of fentanyl toward rapid identification at the micromolar concentration.

RTILs have been shown to improve the behavior of electrochemical processes and thus enhanced performance of electrochemical assays.[24] The RTIL $[C_4C_1pyrr][NTf_2]$ was chosen for use in these proof of concept experiments as it is a hydrophobic ionic liquid which minimizes ingress of water to the electrode surface, thereby allowing wider electrochemical windows to be applied. In addition, the cation, $[C_4C_1pyrr]^+$, is large and bulky, which results in a large RTIL/electrode interface and its asymmetric and nonplanar nature provides sizable cavities, which should aid adsorption of the target materials. Furthermore, $[C_4C_1pyrr][NTf_2]$ has proven efficacy in enhancing the performance of electrochemical sensors and has shown enhanced sensitivities over other ionic liquids for sensing applications for other target analytes.[25−27]

When comparing the CSWV performed with bare SPCE and SPCE modified with $[C_4C_1pyrr][NTf_2]$ (Figure S1), the RTIL-modified SPCE demonstrated greater peak currents (i.e., sensitivity) for all redox peaks. Such sensitivity enhance-

ment reflects the ability of IL-modified voltammetric electrodes to preconcentrate target analytes and promote their electron transfer.[24,28] Because of this enhancement, SPCEs modified with $[C_4C_1pyrr][NTf_2]$ were used throughout this work.

CSWV and CV were then used to characterize the electrochemical fingerprints of fentanyl. A single oxidation peak (A_1) is observed at around +0.560 V in the first anodic scan with both CV and CSWV (Figure 2A and C,
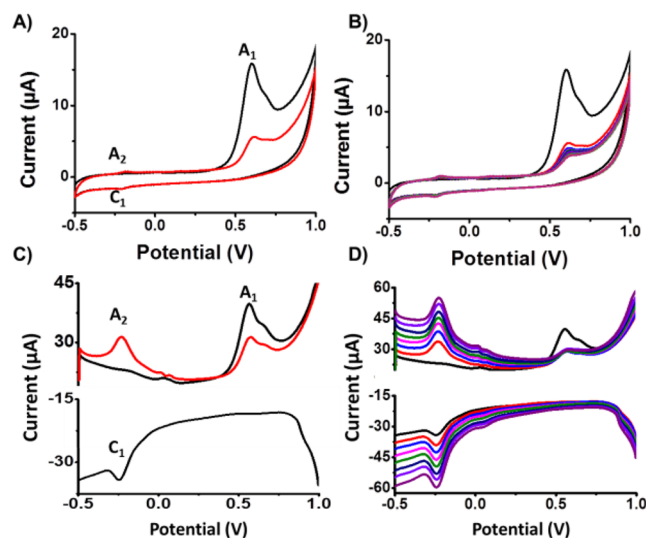
Figure 2. Electrochemical signatures of fentanyl (50 μM) in phosphate buffer (0.1 M, pH 7.4) using CV and CSWV. (A) First two CV scans, scan 1 (black) and scan 2 (red); (B) 15 CV scans; (C) CSWV (first cyclic scan (black), second anodic scan (red); (D) 15 CSWV scans (only every second cyclic scan is shown to clarify and illustrate the trend).

respectively). Closer examination of this peak indicates that this anodic signal involves two poorly resolved peaks that appear as a single peak with a shoulder. Such oxidation process is irreversible, evidenced by the absence of a related peak in the subsequent cathodic scans. This is comparable to results observed for a fentanyl analogue, sufentanil, which has previously demonstrated irreversible oxidation at +0.560 V via DPV using SPCE.[20] This presence of an oxidative process for both fentanyl and sufentanil indicates that electrochemical techniques could offer a broad spectrum presumptive screening test for both N-acyl (e.g., fentanyl) and piperidine-modified (e.g., sufentanil) forms of synthetic opioids.

Following the first anodic scan, a reduction process at −0.235 V (C_1) is observed in the subsequent cathodic scan. This product displays a reversible reduction and oxidation, appearing in all subsequent anodic scans (−0.227 V; A_2) when using CV and CSWV (Figure 2B and D, respectively). This product is dependent on the initial oxidative reaction of fentanyl and is not observed in CV or CSWV undertaken between −0.5 and 0.3 V, until or after the oxidation reaction occurs (Figure S2). This is the first reported observation of this product and provides an important component of the new fentanyl electrochemical signature developed in this study.

Table 1 presents a more detailed analysis of the position and size of the peaks for the electrochemistry of fentanyl from repeated CSWV. The A_1 peak current decreases for each cycle of CSWV, as expected for an irreversible reaction, with fentanyl

Table 1. Calculated Peak Ratios, Amplitude, and Peak Positions for 15 Cycles of CSWV for Fentanyl (50 μM)

scan	ΔE (V) (E_{A2}/E_{C1})	Δi (μA) (i_{A2}/i_{C1})	Δi (i_{C1}/i_{A2})	ΔE (V) (E_{A1}/E_{A2})	Δi (μA) (E_{A1}/E_{A2})	Δi (i_{A1}/i_{A2})
1						
2	0.011	12.743	0.931:1	0.795	0.066	1.010:1
3	0.011	15.377	0.892:1	0.791	−2.757	0.660:1
4	0.011	17.955	0.834:1	0.791	−5.531	0.435:1
5	0.015	19.567	0.842:1	0.795	−6.584	0.379:1
6	0.011	20.996	0.847:1	0.791	−7.46	0.343:1
7	0.011	22.038	0.815:1	0.791	−8.457	0.303:1
8	0.011	23.363	0.836:1	0.795	−9.206	0.276:1
9	0.011	23.922	0.818:1	0.795	−9.729	0.260:1
10	0.011	25.227	0.805:1	0.795	−10.819	0.225:1
11	0.015	25.127	0.850:1	0.791	−10.197	0.249:1
12	0.015	26.353	0.789:1	0.791	−12.119	0.177:1
13	0.015	26.975	0.804:1	0.791	−12.209	0.183:1
14	0.015	26.893	0.846:1	0.795	−10.983	0.246:1
15	0.015	28.011	0.806:1	0.795	−13.153	0.151:1

being consumed at the surface of the working electrode. Conversely, the Δi ratio for the C_1 and A_2 peaks increases with each cycle, consistent with continued reduction of the fentanyl oxidation product while depleting the fentanyl source. The difference in peak position (ΔE) between C_1 and A_2 is only 11−15 mV (Table 1), providing evidence of a reversible, surface confined electrochemical process.[29]

CSWV is the optimal technique for rapid analysis of fentanyl, demonstrating enhanced sensitivity and peak resolution over CV. This is consistent with previous studies using CSWV for detecting and identifying a range of other target analytes.[21,30,31] The combined characteristics of the anodic and cathodic signals from fentanyl using only two CSWV cycles (three combined SWV scans) provides rich information that can serve as a distinct electrochemical signature. This electrochemical signature (Figures 2C,D), coupled with the fast scanning of CSWV, allows characteristic peak information (Table 1) to be obtained rapidly. The entire process can be easily automated by existing analysis software and can be utilized for confirming the presence of fentanyl. Furthermore, since each SWV scan takes only 20 s to perform, the two CSWV cycles needed to generate the unique fentanyl signature take only 60 s to perform. Such operation can thus facilitate rapid screening, and identification of fentanyl in 1 min.

The ionic liquid-modified SPCE sensor performance was assessed using CSWV with sequential 10 μM additions of fentanyl. A complete cycle of anodic, cathodic, and second anodic scan was then performed after each addition, as previously demonstrated in Figure 2C. Focusing on the second anodic scan, it was observed that the A_2 peak current increases with increasing concentration of fentanyl (Figure 3A,B). A plot of peak current for the second anodic scan A_2 peak at different concentrations of fentanyl (Figure 3C) demonstrates a linear relationship ($R^2 = 0.997$). Conversely, the A_1 peak within the second anodic scan demonstrates minimal increase due to the irreversible oxidation of fentanyl during the initial anodic scan, as expected. A comparable experiment was therefore performed using linear SWV where a single anodic scan was performed after each addition of fentanyl. This results in increasing the peak current for both the A_1 and A_2 peaks; however, the increased currents of both peaks were not linear relative to fentanyl concentration (Figure S3).
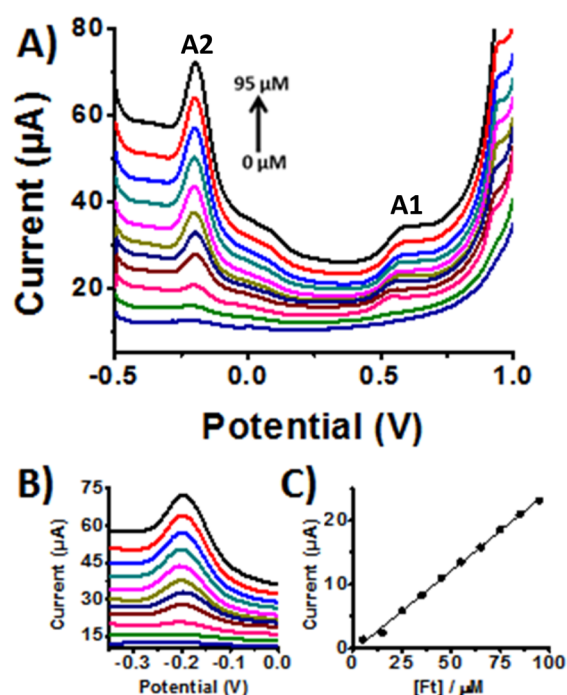

Figure 3. CSWV response of ionic liquid-modified SPCE to increasing concentrations of fentanyl. (A) Second anodic scan after each addition of fentanyl; (B) zoomed plot of the A_2 peak; and (C) corresponding plot of A_2 peak height versus fentanyl concentration with linear trend line ($R^2 = 0.997$).

The measurable detection limit using the current system is 5 μM using two cyclic scans. However, the sensitivity of the system could be substantially enhanced by performing repeated CSWV scans to exploit growth of the A_2–C_1 peak, in addition to further modification of the structure of the working electrode, for example, through the addition of nanomaterials in future work. Modification of the RTIL, for instance, RTIL, through variation of alkyl chain lengths or addition of other functionalities to further enhance the RTIL/SPCE interface and the RTIL/analyte interactions may also be beneficial to increase performance of the sensor.

3.2. Electrochemical Characterization of Fentanyl Metabolites, Norfentanyl and 4-ANPP. Fentanyl is metabolized *in vivo* to a number of products including
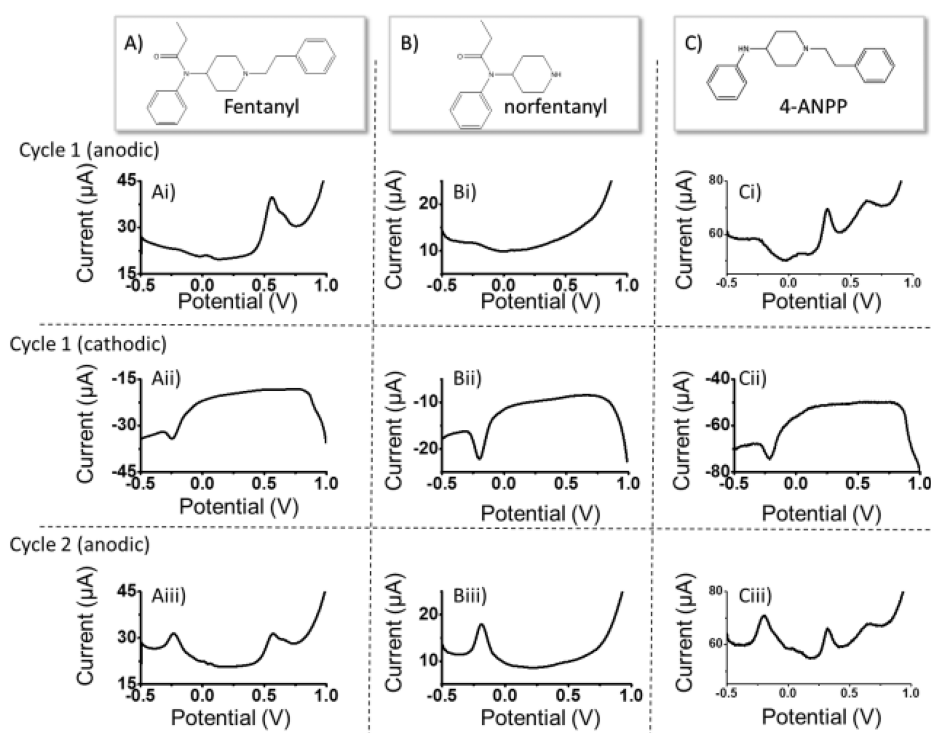
Figure 4. CSWV response of fentanyl in comparison to norfentanyl and 4-ANPP; 50 μM of each analyte was used in each measurement.

norfentanyl and 4-anilino-N-phenethylpiperidine (4-ANPP).[32,33] To facilitate the interrogation of human physiological samples as well as any other suspicious samples by utilizing electrochemical sensors, it is therefore important that these metabolites can be detected. Furthermore, characterization of the electrochemistry of these substances could provide useful analytical information and assists in the understanding the electrochemical mechanism observed for fentanyl under CSWV conditions.

No peaks were observed in the initial anodic scan for norfentanyl (Figure 4 Bi). The C_1 and A_2 peaks previously observed for fentanyl (Figure 4A) at −0.235 V and −0.227 V, respectively, are however observed in subsequent cathodic and anodic scans (Figure 4Bii and Biii, respectively). The lack of any peaks in the initial anodic scan for norfentanyl compared to fentanyl (Figure 4Ai) implies that the irreversible fentanyl oxidation reaction (associated with Peak A_1) results from the electrochemical reaction of fentanyl to produce norfentanyl. This would most logically be due to the oxidative N-dealkylation of the piperidine group. This would generate the unfunctionalized piperidine found in norfentanyl that could undergo reversible oxidation and reduction and hence the emergence of the reversible cathodic peak. *In vivo*, this N-dealkylation reaction occurs naturally via the enzyme cytochrome C_{450} and typically requires high potentials to achieve electrochemically.[34] Parallel studies have however demonstrated that potential cycling via SWV can be used to mimic enzymatic N-dealkylation processes at low oxidative potentials supporting this hypothesis.[35]

The electrochemical signature of 4-ANPP is more complex, displaying two irreversible oxidative peaks at +0.323 V and +0.615 V in the initial anodic scan (Figure 4Ci). These oxidation processes are then followed by the appearance of the reversible −0.235 V peak in the subsequent cathodic scan (Figure 4Cii). Given that the reversible cathodic peak is

present with fentanyl, norfentanyl, and 4-ANPP, at an identical position it is likely that the reversible redox reaction at negative potentials is associated with a common group in all three compounds. Since oxidative N-dealkylation of the piperidine can still occur in 4-ANPP to generate the piperidine group, this further supports the hypothesis of electrochemical oxidative N-dealkylation.
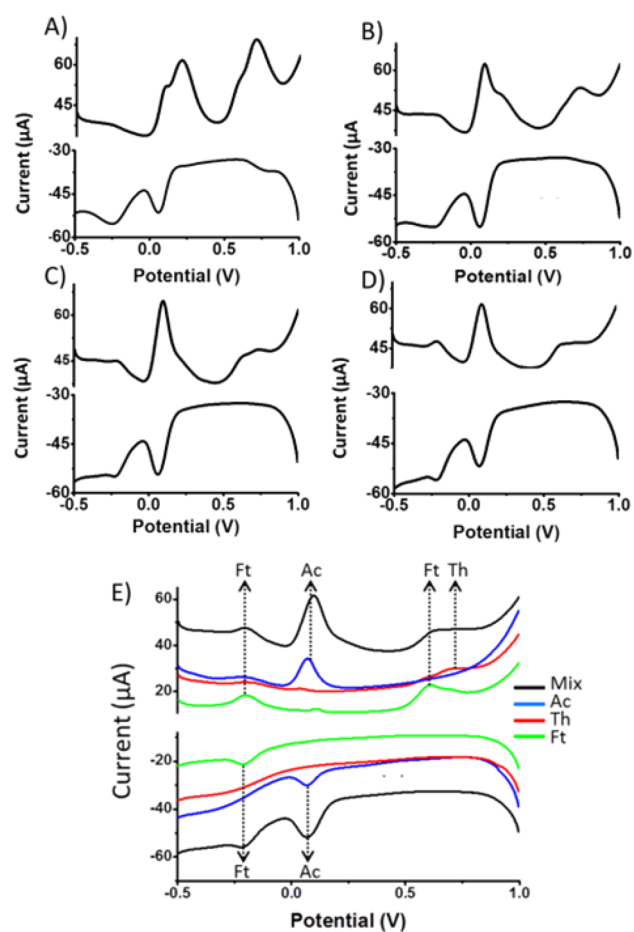
Neither of the two irreversible oxidative peaks at +0.323 V and +0.615 V that occur in the initial anodic scan for 4-ANPP appear in norfentanyl. This implies that they are both associated with the initial oxidative N-dealkylation process and are thus associated with the same oxidative pathway associated with removal of the alkyl chain. Without analysis of additional compounds it is not possible to confirm the mechanism by which this occurs. However, it is possible that the two peaks observed in 4-ANPP are simply the result of better separation of the two poorly resolved peaks observed for the fentanyl A_1 peak. The separation of these overlapping peaks could be due to the different electronic effects in the compound because of the loss of the propionyl group and the resulting, accessible, secondary amine. These effects could cause enhanced intermolecular interactions (e.g., H-bonding), which would lower the oxidative potential associated with any subsequent additional oxidations after the oxidative N-dealkylation of the piperidine.

Further analysis of additional chemicals would need to be performed to determine the exact origin of these peaks, and if this hypothesis is correct, which is outside the scope of this current study. However, for the goal of this study it is important that both physiological metabolites of fentanyl can be readily detected using the CSWV method thus supporting the use of this approach for physiological samples in future studies.

3.3. Electrochemistry of Mixed Samples Containing Common Cutting Agents. Illicit drug supplies are likely to

be contaminated by multiple cutting agents, which have the potential to act as sensor interferents.[36] To simulate this in lab conditions, the common cutting agents caffeine, glucose, acetaminophen, and theophylline were used to test the sensor performance in the presence of these compounds. The electrochemical signatures of each material were initially characterized at a concentration range between 10 μg mL^{-1} and 50 μg mL^{-1} using CSWV (Figure S4). No electrochemical peaks were observed for glucose or caffeine, although caffeine is known to have electrochemical activity at higher applied potentials.[37] Irreversible oxidation of theophylline (+0.731 V) and reversible reduction and oxidation of acetaminophen (+0.088 V) were observed (Figure S4), in agreement with early studies.[38,39]

To simulate a scenario that may be encountered when analyzing an illicit drug street sample, a mixture containing theophylline, acetaminophen, and fentanyl (10 μg mL^{-1} respectively) was then analyzed using the RTIL functionalized SPCE by CSWV (Figure 5). This analysis showed that the constituents of this mixture interact with each other during initial cycles generating doublet anodic peaks at +0.204 V and +0.699 V of CSWV. Cathodic peaks are more defined at +0.065 V and −0.235 V that are likely to correspond to acetaminophen and fentanyl, respectively. Over subsequent cyclic scans, the anodic peaks shift then remain stable at potentials that can be associated with acetaminophen and fentanyl. It is likely that the broad peak at +0.615 V is composed of products derived from both fentanyl and theophylline. This is shown more clearly by overlay of the anodic and cathodic signatures expected for each individual material in comparison to the mixture (Figure 5E). It is clear that CSWV can yield detailed information regarding the chemical makeup of such mixtures, and hence toward the drug provenance. Overall, this demonstrates that CSWV signatures could be utilized to identify and discriminate both fentanyl and other cutting agents in sample mixtures, indicating great promise as an in-field screening tool.

4. CONCLUSIONS

We have demonstrated that the coupling of CSWV and low-cost RTIL-modified electrochemical strips leads to distinct redox signatures of fentanyl and to rapid identification of the drug. The distinct features of such electrochemical signature have been identified and characterized. The addition of RTIL on to the sensing surface results in higher sensitivity and improved selectivity toward identifying the target drug. Such CSWV operation offers distinct advantages over pulse voltammetry and cyclic linear-sweep voltammetry for such rapid identification and trace detection of the drug. The combined characteristics of the anodic and cathodic signals of fentanyl during the initial three SWV scans (two cycles), including the peak ratios and separations, thus provide rich information that leads to a distinct electrochemical signature. Some components of this electrochemical fingerprint are shared by key physiological metabolites and are robust in the presence of other substances frequently found within seized illicit drug samples. Evidence to support the further development of this sensor toward field detection of opioids in environmental and physiological samples is therefore provided. Such development will further enhance the reliability of decentralized field detection of fentanyl and will facilitate on-site investigations and rapid field identification of this important class of drug. Current efforts in our laboratories are aimed at critical large-scale validation of the new electrochemical strip using different illicit drug and biofluid samples. Such critical evaluation will be reported in the near future. Considering the fentanyl range in illicit drug samples,[40] and the sensitivity and selectivity of our sensor, it is expected that the developed sensor can detect Fentanyl in such drug samples.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.analchem.9b00176.

CSWV, CV, linear SWV figures (PDF)

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Figure 5. Electrochemistry of a mixture of fentanyl, acetaminophen and theophylline using CSWV (10 μg mL^{-1} of each analyte). (A−D) Data from 1st cyclic scan (encompassing sequential anodic and cathodic SWV scan) to 4th scan, respectively; (E) 4th cyclic scan from the mixed sample (black) in comparison to the 1st cyclic scan of acetaminophen (blue) and theophylline (red) and second scan of fentanyl (green); 10 μg mL^{-1} of each analyte.

Author Contributions

‖S.A.G. and L.J.H. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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