Application Note 410000012-A01

Rapid Detection of the Low Dose API in Xanax Using Surface-Enhanced Raman Spectroscopy for Anti-Counterfeiting Purposes

The emergence of counterfeit prescription drugs has become a concern for the pharmaceutical industry. Counterfeit drugs are fraudulently manufactured and/or mislabeled to appear genuine. These drugs usually contain no active pharmaceutical ingredient (API) and instead may contain ingredients that are highly potent or dangerous[1,2]. These counterfeit drugs are often manufactured to appear like the genuine prescription drug (Figure 1a). Recently, fake Xanax containing the highly potent opioid fentanyl has accounted for several overdoses in the US[3]. Due to the prevalence of these potentially dangerous counterfeits, it is necessary to develop a technique that can quickly confirm the identity of a suspected fake drug. Because of the low concentrations of APIs found in pharmaceutical drugs, normal Raman spectroscopy is typically not sensitive enough to detect the API from the surface of a pill. In this study we develop a surface-enhanced Raman spectroscopy (SERS)-based approach to identify a low-dose (<0.2% w/w) of the API alprazolam in a Xanax tablet using a handheld Raman spectrometer. If no SERS peaks consistent with alprazolam are observed from a Xanax tablet, the pill is a suspected fake. The method demonstrates the power of SERS to quickly verify the presence of alprazolam in the tablet for anti-counterfeiting purposes.

Xanax

Xanax is a prescription pharmaceutical drug with alprazolam (Figure 1b) as the API. It is used to treat anxiety and panic disorders. A typical Xanax tablet can contain 0.25 mg, 0.5 mg, 1 mg or 2 mg of alprazolam. The excipients, or inactive ingredients, are a composite of cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate[4].

Fentanyl

Fentanyl (Figure 1c) is a synthetic opioid medication. Considered the most potent painkiller on the market (it is 50 to 100 times more potent than morphine[5]), fentanyl is prescribed by doctors for pain management or as part of anesthesia to help prevent pain after surgery or other medical procedures. Increasingly, fentanyl is being manufactured illicitly and sold on the streets as heroin or Xanax, causing a spike in deaths due to fentanyl overdoses. Due to the high potency of fentanyl, fentanyl-containing drugs in the field are usually found in salt forms such as acetyl fentanyl or fentanyl citrate.

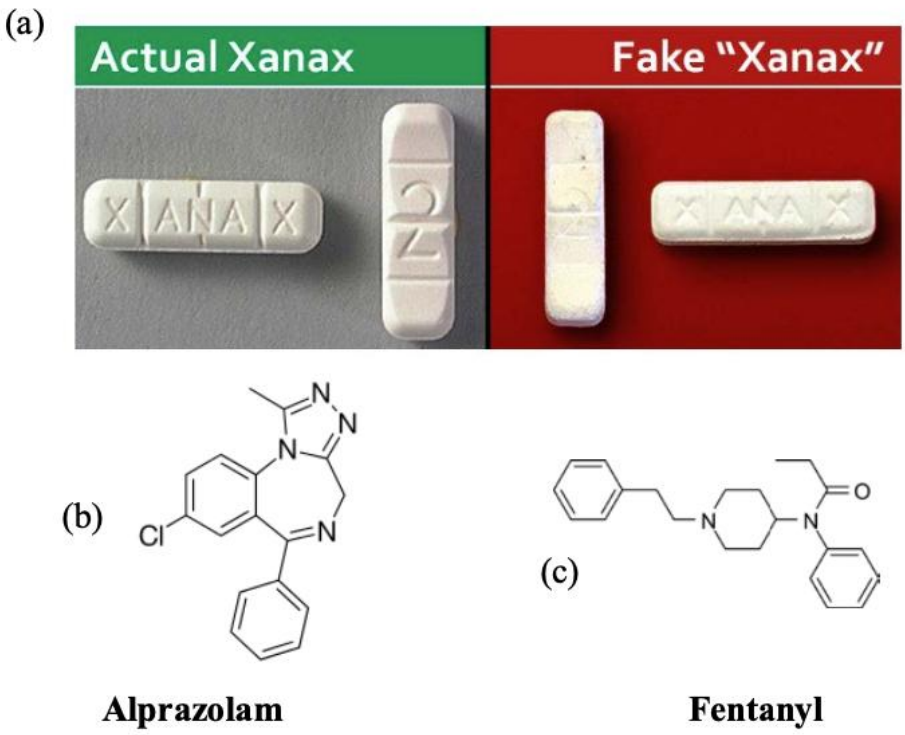

Figure 1. (a) Genuine and fake Xanax tablets containing the chemicals (b) alprazolam (API in Xanax) and (c) fentanyl, respectively

Find more information in the video:

EXPERIMENTAL

Raman spectroscopy was used to identify the low dose of alprazolam in a Xanax tablet. A B&W Tek TacticID handheld Raman spectrometer with 785-nm laser excitation along with a TacPac adaptor for SERS samples (see Figure 2) was used for verification of the method.

Figure 2. TacticID handheld Raman spectrometer with 785-nm laser excitation and TacPac adaptor

The samples tested in this work include a purchased Xanax tablet containing 0.25 mg of alprazolam and fentanyl from confiscated lab-confirmed samples courtesy of our collaborator at a police department. Approximately 1/4 of a Xanax tablet (~30 mg) was placed in a 2.0 mL plastic centrifuge tube. Then, 0.5 mL of acetone was added to the centrifuge tube. The tube was shaken until the sample dissolved and the solution looked noticeably cloudy. The paper-based SERS substrate was dipped into the solution and allowed to sufficiently interact with the sample and the solution (~30 s). The SERS substrate was then placed in the TacPac adaptor for analysis with the TacticID. To account for sample heterogeneity within the SERS active region, at least 3 different spots were analyzed on each SERS substrate. Automated integration times for the scans ranged from 15-30 s.

TEST RESULTS

Direct Raman measurement of Xanax

Figure 3 presents the Raman spectrum acquired directly from the surface of a Xanax tablet (a) overlaid with the Raman spectrum of lactose (b). Observed Raman peaks at 356 cm^{-1}, 436 cm^{-1}, 476 cm^{-1}, 1088 cm^{-1}, 1120 cm^{-1}, and 1264 cm^{-1} in spectrum (a) are consistent with lactose. No peaks consistent with alprazolam were observed in the Raman spectrum from the surface of the tablet. The direct measurement of a Xanax tablet on the TacticID returns a spectral correlation to lactose with an HQI of 86.7, indicating that a direct handheld Raman measurement cannot identify the active ingredient in Xanax from the surface of the pill.

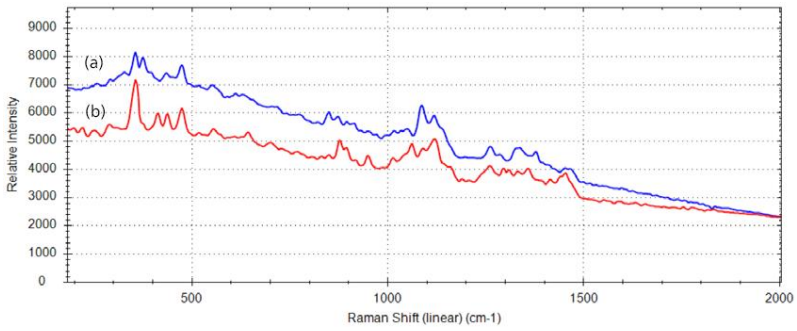

Figure 3. Spectra from (a) direct handheld Raman measurement of Xanax tablet and (b) direct handheld Raman measurement of lactose

Detection of Alprazolam in Xanax

Figure 4 presents the Raman spectrum of pure alprazolam (a) and the SERS spectrum obtained from Xanax (b). Observed SERS peaks at 688 cm^{-1}, 1000 cm^{-1}, 1132 cm^{-1}, 1160 cm^{-1}, 1312 cm^{-1}, 1380 cm^{-1}, 1484 cm^{-1}, 1568 cm^{-1} and 1592 cm^{-1} are consistent with the Raman spectrum of pure alprazolam. Figure 5 shows typical SERS spectra obtained from Xanax excipients (cellulose, lactose, corn starch, and magnesium stearate). Due to the low solubility of the excipients in acetone, no characteristic Raman signatures from these materials are captured in the Xanax SERS spectrum. Although alprazolam makes up <0.20% (w/w) of the Xanax tablet, the SERS substrate sufficiently enhances the Raman signal so that it is possible to obtain signal consistent with the API despite the greater concentration of excipients in the tablet. This demonstrates the method's high selectivity for the API and the ability of the SERS testing of the samples on the substrate to identify a low-dose of alprazolam.

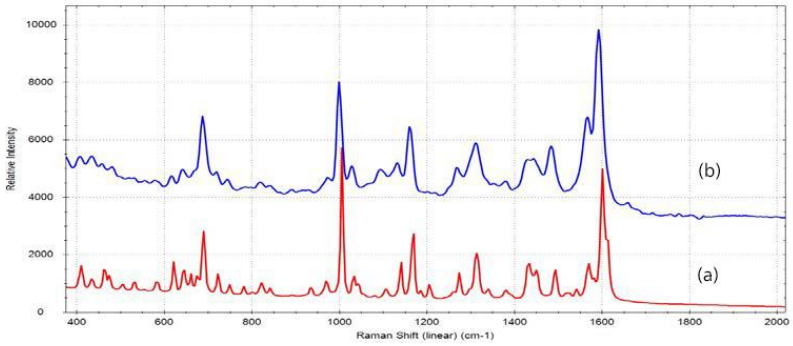

Figure 4. (a) Raman spectrum of pure alprazolam and (b) SERS spectrum from Xanax

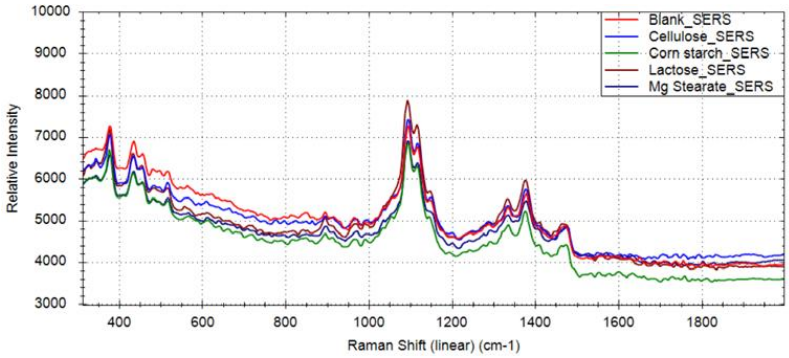

Figure 5. SERS spectra of a blank substrate, cellulose, corn starch, lactose, and Mg stearate

Detection of Fentanyl

In order to detect fentanyl often substituted for alprazolam in fake Xanax, the SERS method was also applied to fentanyl detection. Figure 6a presents the SERS spectrum from a fentanyl sample. A strong peak at 1000 cm^{-1} assigned to the ring-breathing mode and a small peak at 1029 cm^{-1} are common to the SERS spectra for both alprazolam and fentanyl. However, the alprazolam signal from Xanax (Figure 6b) has unique peaks at 688 cm^{-1}, 1480 cm^{-1}, 1568 cm^{-1}, and 1592 cm^{-1} that are not observed in the fentanyl spectrum. With the proper algorithm, fentanyl and alprazolam can be distinguished spectroscopically despite some common peaks. For anti-counterfeiting purposes, if peaks consistent with alprazolam are not observed in the SERS spectrum from a Xanax pill, then the pill is considered a suspected fake.

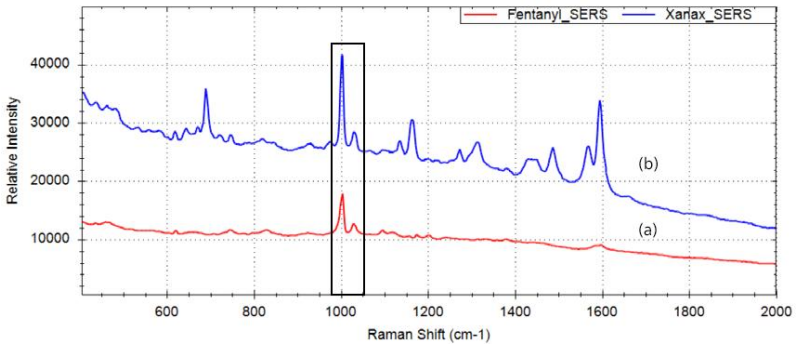

Figure 6. SERS spectra of (a) fentanyl and (b) Xanax

Identification of Xanax

A correlation coefficient algorithm was used for spectral comparison to identify an unknown spectrum against a library spectrum. The correlation coefficient HQI (Hit Quality Index) for the unknown scans compared to a library spectrum is calculated using the least square dot product of mean centered unknown spectrum and the library spectrum, represented by the equation:

$$HQI = \frac{(Library \cdot Unknown)^2}{(Library \cdot Library)(Unknown \cdot Unknown)} \text{ x } 100$$

HQI values range from 0 to 100, with 100 representing a perfect match. The average HQI correlation to a library spectrum for three unknown scans of fentanyl and of Xanax ingredients is listed below in Table 1.

Table 1. Matching Results

Material	Results & Average HQI (n = 3)
Fentanyl	Match to Fentanyl (HQI = 82.33)
Xanax	Match to Alprazolam (HQI = 91.00)
Lactose	No match
Cellulose	No match
Mg stearate	No match
Corn starch	No match

CONCLUSIONS

A SERS-based method was developed for the detection of low doses of alprazolam in a Xanax tablet. The method demonstrates high selectivity for the alprazolam in Xanax despite the extremely low dose. A handheld TacticID Raman spectrometer with onboard software was able to discriminate between the SERS spectrum of the API alprazolam and the spectra from the Xanax excipients. For anti-counterfeiting purposes, if no peaks consistent with alprazolam are observed in the SERS spectrum from a Xanax pill, then the pill is considered a suspected fake.

The SERS spectrum of fentanyl can also be identified by the TacticID, allowing the detection of fentanyl when it is used in substitute of alprazolam. The sample preparation for the SERS analysis is simple and can be easily performed by field officers. The ability to quickly identify the presence of alprazolam in a Xanax tablet or potential harmful materials such as fentanyl is a valuable tool for law enforcement and the pharmaceutical industry to combat the prevalence of counterfeit pharmaceutical drugs.

FURTHER READING

Related application notes

B&W Tek TacticID for Narcotics Identification

Other related documents

Raman vs SERS... What's the Difference?

REFERENCES

1. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/
2. https://addictionresource.com/drugs/the-dangers-of-fentanyl/
3. https://www.dea.gov/docs/Counterfeit%20Prescription%20Pills.pdf
4. https://www.xanax.com/
5. https://www.drugabuse.gov/drugs-abuse/fentanyl

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CONFIGURATION

TacticID GP Plus Handheld Raman Spectrometer

The TacticID-GP Plus is a field-ready, handheld spectral analyzer designed for rapid, nondestructive chemical identification. This allows the reduction of operational uncertainty and response time. Featuring an intuitive workflow and touch screen, samples can be nondestructively analyzed through opaque and transparent packaging. The sample threat level is displayed prominently to the users, e.g. security staff, emergency services (such as law enforcement authorities), customs and border guards as well as bomb disposal squads, and hazmat teams, allowing them to act quickly with minimal sample contact. The TacticID-GP Plus utilizes proven Raman spectroscopy, allowing users to obtain real-time identification of samples with threat level and GHS and NFPA704 safety information clearly displayed.

TacticID N Plus Handheld Raman Spectrometer

The TacticID® –N Plus is a field-ready handheld Raman Spectrometer specifically designed for non-contact forensic analysis of narcotics, pharmaceutical drugs, cutting agents, and their precursors by law enforcement personnel.

Featuring an intuitive workflow and touch screen, samples can be nondestructively analyzed through opaque and transparent packaging. The sample threat level is displayed prominently to the users, e.g. security staff, emergency services (such as law enforcement authorities), customs and border guards as well as bomb disposal squads, and hazmat teams, allowing them to act quickly with minimal sample contact. The TacticID-N Plus utilizes laboratory-proven Raman spectroscopy, which allows users to obtain identification of illicit substances in real time without ever compromising the integrity of the sample or the chain of evidence.

The TacticID-N Plus comes with a comprehensive library of over 1000 substances as standard. Additionally, users have access to regular library updates in order to continuously maintain up-to-date identification capabilities and stay ahead of emerging narcotics.

TacPacTM Adapter

SERS analysis adapter for use with TacPacTM-P SERS substrates.