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Vibrational Spectroscopy of Pain Relievers: Traditional and Remote Raman Techniques

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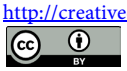

Abstract

The application of vibrational spectroscopy in the pharmaceutical industry is widely investigated, from the quality assurance of the product during the production process control to the final products' quality control and the authentication of products on the markets. This study focuses on non-contact and noninvasive detection and identification of pain-relievers at 1 - 5 meters standoff distances. The specimens analyzed include standard laboratory-grade active ingredients and commercially available pain relievers in powder, solid and liquid forms. All the remote measurements captured revealed the Raman signatures of the specimens, with varying peak intensities. To correlate the band intensities captured with the standoff distances between the laser source and the specimens, the intensity ratios of the two prominent peaks of the laboratory grade reference active ingredient (1607 and 1319 cm^{-1}) normalized with 1319 cm^{-1} are used. The results of the study suggest the viability of standoff Raman spectroscopy for routine monitoring and identification of pharma- ceuticals, including counterfeit pain relievers.

Keywords

Raman Spectroscopy, Acetaminophen, Aspirin, Standoff Raman, Vibrational Spectroscopy, Pain Relievers

1. Introduction

Raman spectroscopy is a powerful technique that uses vibrational energy levels of materials of interest to create a spectrum unique to every material. This uniqueness could be displayed in terms of the spectral position and intensity of various Raman bands. Conventional Raman spectroscopy is widely used as a research tool for routine quality control, analysis, and characterization of mate-

rials. This is likely due to the fact that conventional Raman spectroscopy involves analyzing samples from a close distance of a few millimeters. Standoff Raman spectroscopy involves analyzing samples from distances of a few centimeters up to hundreds of meters and has recently proven to be a very valuable tool in detecting explosives, atmospheric pollutants, and minerals [1] [2]. Raman spectroscopy has also been used in food science, to detect adulterants used in food [3] [4] [5] [6]. In earlier work, the technique has been demonstrated to detect commercially motivated adulteration of extra virgin olive oil with 10 percent canola, grape seed, and sunflower oils, without removing the oil from the container [6]. Using an 11-inches telescope integrated with a 785 nm laser source placed at 250 meters standoff distance from the specimen, Sadate *et al.*, detected nitrates powder [7]. One of the benefits of the remote Raman spectroscopy technique, demonstrated here in the present work, is that it is contactless with the sample, the advantage of collecting the Raman spectra remotely without removing the drug from the containers. As most of the containers for pharmaceutical drugs/pain relievers are transparent, the laser beam can easily pass through the containers and capture the Raman spectra of the drugs. This makes the technique viable for routine monitoring and identification of pharmaceuticals, including counterfeit medicines. The application and efficiency of the remote Raman spectroscopy system for real-time detection and identification of explosives and other hazardous chemicals of interest, air pollution monitoring, and planetary and geological mineral analysis at various standoff distances have been demonstrated [1] [2] [3] [4]. However, the application of the standoff Raman technique for the characterization of pharmaceutical drugs has not been explored. This work demonstrates the adequacy of the traditional and standoff Raman techniques for detecting, identifying, and analyzing acetaminophen-containing drugs and over-the-counter pain relievers.

In the pharmaceutical industry, Raman spectroscopy has been used for industrial process monitoring, quality control of products, detection and identification of counterfeit medicines. The technique has several benefits, including short acquisition time, no complex sample preparation required, non-destructive, non-invasive, and in cases the container or package is transparent, the spectra could be acquired without removing the material from their package [7] [8] [9] [10] [11]. Yves Roggo *et al.*, used chemometrics coupled with Raman spectroscopy to discriminate counterfeits pharmaceutical tablets [12]. The authors developed a calibration curve to identify families of different tablets with calibration of the same active pharmaceutical ingredient (API) but containing different concentrations to discriminate counterfeit drugs from genuine ones [8] [12]. The application of vibrational spectroscopy in the pharmaceutical industry is broad, including process monitoring and control, authenticating drugs, and identifying drugs inside the packages [9] [10]. It has also been used for investigating photo-sensitivity and the degradation of active ingredients in pharmaceutical drugs [13]. Handheld Raman systems can also effectively distinguish falsified pharmaceutical products from authentic active pharmaceutical ingredients

and the authenticity of commercial tablets [10] [14] [15].

2. Literature Review

The application of Raman spectroscopy in the pharmaceutical industry is widely investigated, from the quality assurance of the product during the production process control to the final products' quality control and the authentication of products on the markets [16]. Kim *et al.* (2007) used Raman spectroscopy to measure the concentration of povidone, also called polyvinylpyrrolidone, used as a lubricant in commercially available eye drops. The Raman spectra were collected by launching a wide area laser beam through a low-density polyethylene (LDPE) plastic container. Partial least square regression analysis of the spectra was used to estimate the concentration of povidone, an active pharmaceutical ingredient in a commercial eye wash solution in LDPE bottles.

Chetan *et al.*, used Raman spectroscopy to demonstrate the ability of the system to identify and quantify a mixture of four different drugs (acetaminophen, lidocaine, azithromycin, and epinephrine) and their degradation products [17]. The samples were prepared by grinding to finely powdered particle sizes, vortex mixed and again grounded to improve homogeneity. However, Vankeirbbilck *et al.*, suggested that crushing and grinding specimens can alter the solid state property of materials [8]. High pressure applied to pharmaceutical drugs like aspirin is known to produce new polymorphic phases having different intra- and inter-molecular arrangements, changing the functionality and performance of the drug [18]. The effect of high-pressure phase change and eventual changes in the bonding and the arrangement of the structural groups of polymorphic phases of aspirin with varying chemical and physical properties are studied using micro-Raman spectroscopy [18]. The micro-Raman system described in Crowell *et al.*, is used to examine the stability and detect the bonding and molecular and structural changes resulting due to high-pressure imposed on aspirin [18]. The primary benefit of using Raman spectroscopy in the current study is the fact that no sample preparation and removal of the specimens from the bottle or package is required to acquire the measurements at standoff distances. In some other techniques, for instance, where sample preparation requires grinding, the process changes the properties of the inherent solid states, including the chemical bonding of the active ingredient to be tested [8]. The measurements can be acquired non-invasively without removing the sample from the package or causing any damage to the specimens. However, the intensity of the Raman spectra depends on the color and material of the package or bottles and the distance between the probe and the specimens.

Raman spectroscopy, coupled with multivariate statistical analysis of the spectra acquired from finger marks of suspects in contact with prescription and over-the-counter nonsteroidal anti-inflammatory drug traces, is also used for chemical analysis and criminal investigation of suspects in contact with drug traces [19]. The technique is reported to have tremendous benefits in narrowing

down the pool of suspects for criminal investigation. Xuejia Zhao *et al.*, demonstrated the application of Transmission Raman Spectroscopy (TRS) in the pharmaceutical manufacturing industry coupled with the statistical design of experiment and partial least square model for monitoring the quality of drugs during the production stage [20]. The model developed is used to monitor the pharmaceutical production process and predict the concentration of active ingredients in marketed paracetamol tablets. As compared with the standard spectrophotometry and chromatography, vibrational spectroscopy-based analytical techniques for the detection and identification of commercial drugs/tablets, such as acetaminophen, is advantageous due to the ease in sample preparation and rapid processing and analysis showing the molecular compositions of the specimens [21]. As covered in this section, earlier works reported the viability of vibrational spectroscopy for the analysis and screening of pharmaceutical drugs [1]-[23]. To the best of our knowledge, this is the first study demonstrating the use of standoff Raman spectroscopy to analyze pharmaceutical pain relievers.

3. Methods and Materials

The analytical grade standard acetaminophen with a molecular weight of 151.2 and the molecular and linear formula of $C_8H_9NO_2$ [24], and $CH_3CONHC_6H_4OH$ [25], respectively, was purchased from Sigma-Aldrich, U.S.A. in powder form. The commercial pain relievers containing acetaminophen (liquid acetaminophen 500 mg per 15 mL) and aspirin 325 mg tablets were obtained from local drug stores. As indicated on the product's label, the inactive ingredients of the liquid acetaminophen 500 mg per 15 mL pain reliever include citric acid, high fructose corn syrup, polyethylene glycol, propylene glycol, purified water, saccharin sodium, sodium benzoate, sorbitol and synthetic dyes D & C red # 33 and FD & C red #40. The 325 mg aspirin tablet is a nonsteroidal anti-inflammatory drug (NSAID) containing inactive ingredients such as corn starch, hypromellose, polyethylene glycol, and propylene glycol [26].

The vibrational spectra of the standard and specimens were acquired using conventional and standoff Raman spectroscopy systems. The traditional Raman measurements were collected at an optimum distance of 7 mm and at close contact with the container/bottle, and the remote Raman measurements were captured at distances of 1 - 5 meters. The Raman system used is a portable 785 nm excitation diode laser EZRaman Analyzer (Enwave Optronics EZRaman) consisting of a continuous wave excitation wavelength of 785 nm diode laser with a maximum output power of 400 mW, integrated with a charge-coupled device (CCD) detector coupled to a small spectrometer, which has a spectral resolution of 6 cm^{-1}, and a spectral range of 250 - 2500 cm^{-1}. The laser power for all the measurements was set to about 100 mW at the specimens. For the standoff measurements, a 2-inch refractive telescope focuses the laser light on the sample target and collects the scattered Raman light from the sample back to the spectrometer.

4. Results and Discussions

Figure 1 presents the baseline corrected Raman spectrum of acetaminophen powder captured at 7 mm and at a standoff distance of 1 meter collected with 30 seconds integration time. The result shows strong bands at 383, 643, 791, 850, 1163, 1231, 1273, 1319, 1367, 1558, 1607, and 1644 cm^{-1}, with the bands located at 850, 1231, 1319, 1607, and 1644 cm^{-1} being very prominent. Other weaker Raman bands are located at 320, 457, 496, 596, 619, 703, 962, 1010, 1099, 1252, 1441, 1503, and 1511. The conventional Raman measurements acquired at a distance of 7 mm between the laser tip and the specimens and the spectra captured from the standard acetaminophen powder placed at standoff distances of 1 - 5 meters from the probe identified all the characteristics Raman bands (Figure 1 and Figure 2). One significant difference between the measurements is the variation in peak intensities with the distance between the laser and the specimens.

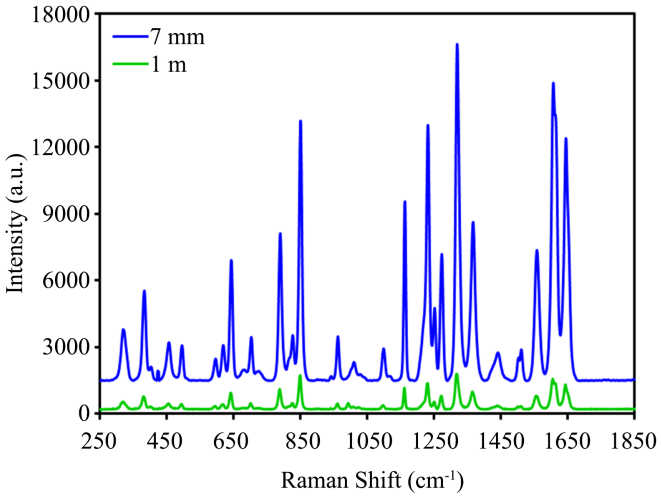

Figure 1. Raman spectra of acetaminophen powder captured at 7 mm (traditional Raman), and at 1-meter standoff distance, collected with 30 seconds exposure time.

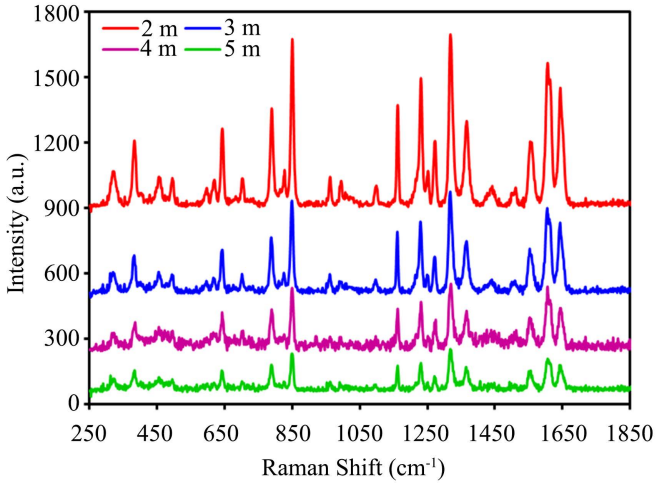

Figure 2. Raman spectra of acetaminophen powder captured at standoff distances of 2 m, 3 m, 4 m, and 5 meters collected with 30 seconds of exposure time.

The correlation between the Raman band intensities with the distances is plotted in Figure 3. The strong characteristics Raman bands located at 791, 858, and 1231 cm^{-1} are attributed to the CNC ring stretching, ring breaching and C-C ring stretching, respectively [17]. The bands at 1319, 1558, 1607, and 1644 cm^{-1}, which are slightly shifted from the bands reported by Chetan *et al*., [17] are assigned to amide III, amide II N-H in-plane deformation, skeletal aryl C-C ring stretching, and amide I modes respectively [11] [20]. The weak bands at 841, 1441, and 1511 cm^{-1}, are assigned to out-of-plane C-H bending skeletal aryl C-C stretch and aryl C-H symmetric bends, respectively [11] [20].

Similar to the acetaminophen standard, Raman spectra of 325 mg aspirin tablets were captured at 15 seconds of integration time (Figure 4). The measurements show strong Raman bands at 417, 542, 632, 696, 743, 777, 1038, 1147, 1252, 1288, and 1602 cm^{-1}. There are also several weak, but discernable bands at 283, 313, 370, 506, 656, 799, 849, 876, 911, 964, 1007, 1217, 1363, 1424, 1478, 1572, 1622, 1720, and 1747 cm^{-1}. Due to the variation in Raman band intensities among the traditional Raman and the remote measurements, the spectra of the aspirin tablets captured at remote distances of 1, 2, and 3 meters collected at 60 seconds integration time are plotted separately (Figure 5). Figure 6 shows the Raman spectra of 500 mg per 15 mL acetaminophen liquid acquired at 120 seconds of integration time, with the probe touching the bottle (without removing the sample from the container). Figure 7 shows the spectra of the same sample placed at standoff distances of 1, and 2 meters from the laser source, collected at 120 seconds of integration time. The results show that Raman bands identifying acetaminophen in the liquid are slightly shifted compared to the bands observed in the reference but are present. The peaks observed in the standard specimen shifted in the liquid specimen include bands at 326, 702, 797, 854, and 1613 cm^{-1}. The other Raman bands represent the presence of the inactive ingredients of the liquid acetaminophen 500 mg per 15 mL pain reliever.

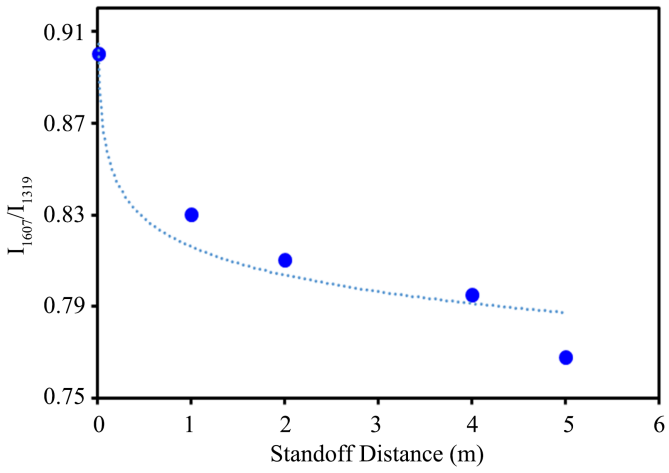

Figure 3. The variation in Raman band intensity ratio versus the standoff distances between the telescope and the acetaminophen powder, measured at 30 seconds of integration time.

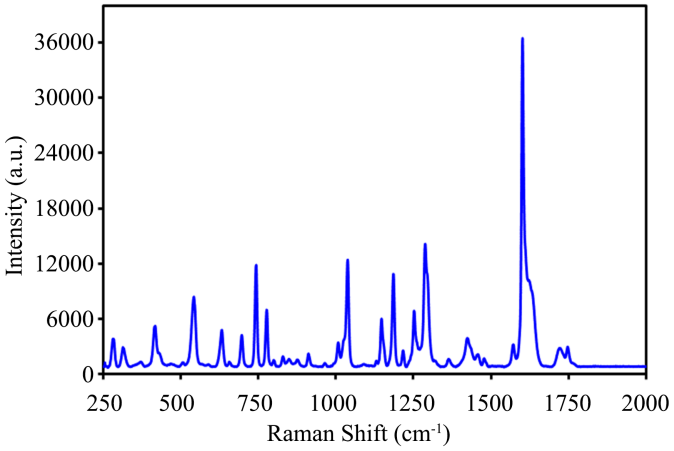

Figure 4. Raman spectra of 325 mg aspirin tablets directly exposed to 785 nm laser light, collected at 15 seconds integration time.

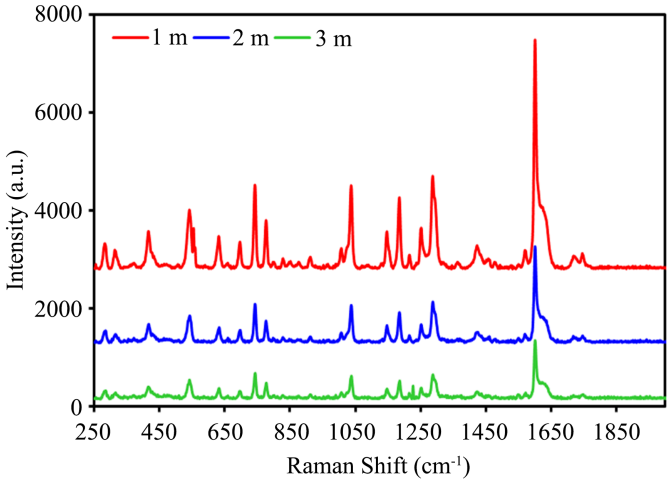

Figure 5. Raman spectra of 325 gm aspirin tablets inside a bottle, captured at standoff distances of 1 m, 2 m, and 3 meters, and 60 seconds of integration time.

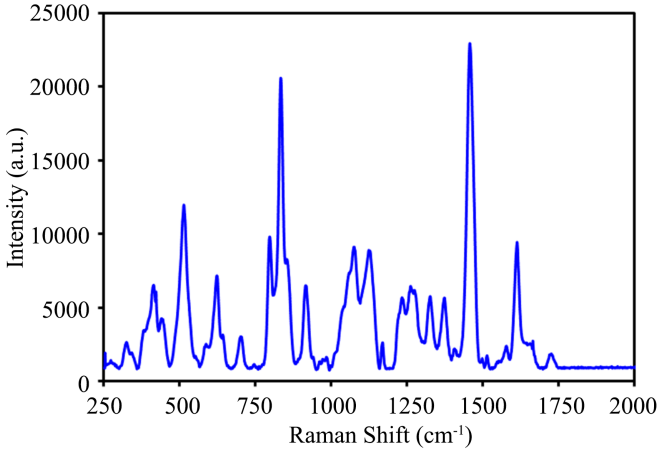

Figure 6. Raman spectra of acetaminophen 500 mg per 15 mL liquid acquired without removing the specimen from the package. The measurement was collected at 120 seconds of exposure time, with the probe touching the container.

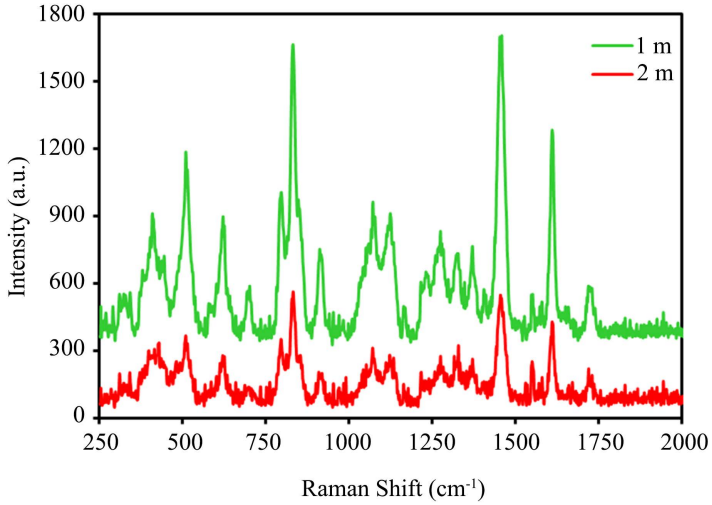

Figure 7. Raman spectra of acetaminophen 500 mg per 15 mL liquid inside the container captured at standoff distances of 1 m and 2 meters from the probe. The measurements were collected at 120 seconds of exposure time, with the probe touching the container.

The standoff Raman results presented in **Figure 2** and **Figure 5** and **Figure 7** suggest the viability of the technique for remote screening and identification of pharmaceutical pain relievers in powder, tablets, and liquid form. To analyze the variation in band intensities of the traditional and the remote measurements, the intensity ratios of the two prominent peaks of acetaminophen reference (1607 and 1319 cm^{-1}) normalized with 1319 cm^{-1} with each data point shown in the chart averaged from 5 measurements. As shown in **Figure 3**, the ratio of the Raman band intensity captured at 7 mm (conventional measurement) is about 0.9 followed by the standoff distances ranging from 1 m to 5 meters. The data points are well-fitted to the logarithmic dependence trend line with an R^2 value of 0.93. The equation of the curve is $y = -0.018\ln(x) + 0.8161$. This equation correlates the intensity ratio of the acetaminophen reference sample with the standoff distances between the probe and the sample.

5. Conclusion

Conventional and standoff Raman measurements of pain-relievers in powder, solid and liquid forms have been accomplished. The traditional Raman measurements were collected at an optimum distance of 7 mm between the specimen and the laser source, and the remote spectra were captured at 1 - 5 meters distances between the laser source and the samples. All the measurements acquired revealed the characteristic spectral signatures of the specimens studied, with varying peak intensities, demonstrating the feasibility of the conventional and standoff Raman spectroscopy for non-invasive and non-destructive detection and identification of pain relievers without removing the specimens from the containers. The results of the pharmaceutical pain relievers in powder form, liquid, and tablets indicated the reliability of the technique for routine checking, detection, and identification of pharmaceutical products in the laboratory and

field setting. The method is efficient, non-destructive, and reproducible results that can be acquired and analyzed in a short period of time.

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Author Contributions

D. R. is an undergraduate student at Alabama State University who participated in the summer research internship program at Alabama A & M University supported by the NASA-MUREP program. A. K. and D. R. conducted the measurements. A. K. originated the idea and wrote the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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