Mater Eng Res, 2023, 5(1): 291-305
DOI: 10.25082/MER.2023.01.005

REVIEW

Unveiling molecular secrets: Raman spectroscopy as a versatile tool for advanced analysis and investigation in forensic science and pharmaceuticals

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Received: September 17, 2023;
Accepted: November 30, 2023;
Published: December 5, 2023.

Citation: Ahmed MD, Maraz KM and Mazumder S. Unveiling molecular secrets: Raman spectroscopy as a versatile tool for advanced analysis and investigation in forensic science and pharmaceuticals. *Mater Eng Ress*, 2023, **5**(1): 291-305.
https://doi.org/10.25082/MER.2023.01.005

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Abstract: The conventional technologies used for identifying, investigating, and analyzing illegal drugs, explosives, and fibers in forensic science often involve destructive methods, preventing re-analysis of evidence. Conversely, a non-destructive approach is crucial for drug characterization, synthesis route development, and identification of counterfeit and adulterated pharmaceuticals. Raman spectroscopy, renowned for its rapid, non-destructive, and cost-effective nature, has emerged as the predominant technique in forensic and pharmaceutical applications. Its inelastic light scattering properties enable drug identification, minimize forensic toxicology and criminalistics, and ensure pharmaceutical product quality. This review explores the analysis of cocaine, RDX, HMX, PETN and TNT in forensic science, where Raman spectroscopy proves invaluable in detecting and quantifying drugs and explosives, deciphering synthesis routes, identifying manufacturing labs, and unveiling trafficking patterns and distribution networks. Additionally, it examines the analysis of acyclovir, ciprofloxacin, and active pharmaceutical ingredients (APIs) in the pharmaceutical industry, offering insights for quality control, combating counterfeit and adulterated products, and facilitating real-time process monitoring. Despite limitations, recent advances in data analysis techniques position Raman spectroscopy as a versatile and promising tool for sample analysis, investigation, and determination in both forensic science and pharmaceuticals, illuminating the path towards enhanced analytical capabilities in these fields.

Keywords: Raman spectroscopy, Forensic analysis, drug and explosive identification, pharmaceutical analysis, drug development, Counterfeit and Adulterated pharmaceuticals

1 Introduction

Raman spectroscopy has emerged as an advanced, noninvasive optical reflection technique, characterized by high spectral resolution, that enables molecular identification and comprehensive investigations of molecular properties. By subjecting molecules to monochromatic light, Raman spectroscopy harnesses the phenomena of inelastic and elastic light scattering, providing invaluable insights into molecular vibrations and yielding a deeper understanding of composition, symmetry, electronic environment, and bonding within the molecule. This analytical method facilitates both qualitative and quantitative analyses of individual compounds, rendering it an indispensable tool in contemporary scientific research [1, 2].

In the realm of forensic science, Raman spectroscopy has garnered significant attention due to its versatility and efficacy in identifying seized drugs, explosives, paints, and fibers. Its applications extend far beyond toxicology and criminology, encompassing the navigation of intricate synthesis labs and the elucidation of distribution routes [2]. By leveraging the distinctive Raman spectral fingerprints of these substances, critical information regarding their structural characteristics can be obtained, thus facilitating their identification, and supporting forensic investigations [3–5].

The pharmaceutical industry has also recognized the immense potential of Raman spectroscopy. With its ability to ensure product quality and mitigate adulteration, this technique plays a pivotal role in maintaining the integrity of pharmaceutical products. By analyzing the Raman spectra of pharmaceutical compounds, it becomes possible to monitor their chemical composition, detect counterfeit or substandard products, and evaluate the presence of impurities or deviations from established quality standards [6–8]. Additionally, Raman spectroscopy

enables real-time process monitoring, enabling optimization of pharmaceutical manufacturing and quality control protocols [9, 10]. (see Figure 1)

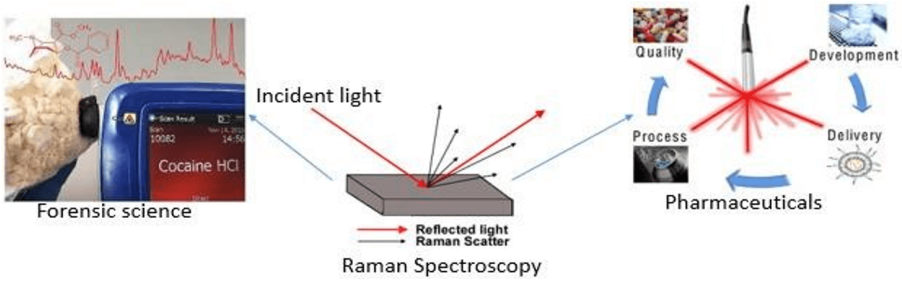


Figure 1 Using Raman Spectroscopy in Forensic science and Pharmaceuticals [5, 10]

This paper aims to provide a comprehensive exploration of advanced Raman spectroscopy, encompassing its underlying principles, methodologies, and diverse analytical applications. By delving into the intricacies of molecular vibrations and the unique spectral signatures they generate, we aim to shed light on the vast potential of Raman spectroscopy as a versatile and powerful analytical tool. Through an in-depth examination of its applications in forensic science, with a specific emphasis on drug analysis, as well as its indispensable role in pharmaceutical quality control, this paper underscores the profound significance of Raman spectroscopy in addressing critical challenges across scientific disciplines.

2 Basic principles (Mechanism and Instrumentation) of Raman spectroscopy

Raman spectroscopy is a powerful tool that utilizes the inelastic scattering of photons by matter to examine molecular structure. When a photon interacts with the functional groups of a molecule, it causes absorption or emission of phonons in the sample, resulting in Raman scattering [11]. The scattered light can be detected by a Raman spectrometer and represents a "chemical fingerprint" of the substances. The energy of the scattered photons varies depending on the vibrational state of the molecule, and the Raman shifts at specific wavelengths can be used to identify functional groups within molecules [7, 12, 13].

In Raman scattering, an incident photon interacts with matter that eventually irradiates with an alternate wavelength than the incident radiation, which is called inelastic scattering. There are two types of inelastic scattering that can occur: stokes scattering (high wavelength) and anti-stokes scattering (low wavelength). In stokes scattering, an excited molecule energized from the incident photon is promoted from the vibrational state to the ground state. In anti-stokes scattering, the opposite process occurs [14, 15]. In addition to providing information about vibrations within a molecule, Raman scattering can also yield information about rotational energy in gases and phonon modes in solids. (see Figure 2)

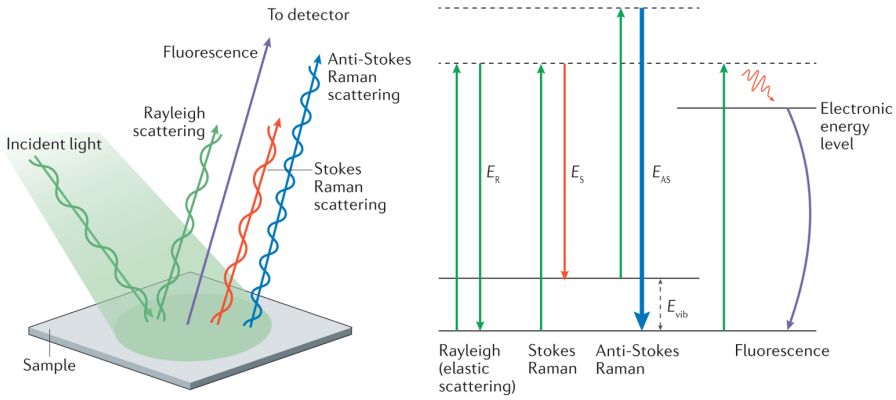


Figure 2 Molecular energy level diagram and Raman effect [16, 17]

Raman spectroscopy is a non-destructive and highly sensitive technique that can be used to probe highly complex molecules, making it a valuable tool in many scientific fields [18]. However due to its low scattering cross-section (∼10-30 molecule cm^{-1}), it is difficult to identify some of the complex structures, even with a high-resolution Raman spectrometer.

A Raman spectrometer is composed of four main parts: a light source, a monochromator, a sample collector, and a detector [19]. The quality of the instrument stability, adequate resolution, and high signal-to-noise ratio are all factors that can influence Raman spectral analysis [19]. Fluorescence can interfere with Raman signals, but the development of efficient FT Raman spectrometers with NIR or red excitation lasers has solved this issue [19, 20]. Extremely sensitive detectors in combination with the pairing of optical fibers and microscopes have also increased the analytical capability of Raman spectroscopy [21]. There are two main methods used to obtain Raman spectra: dispersive Raman spectroscopy and Fourier transform Raman spectroscopy, which differ in their laser sources and the way Raman scattering is measured and analyzed. (see Figure 3)

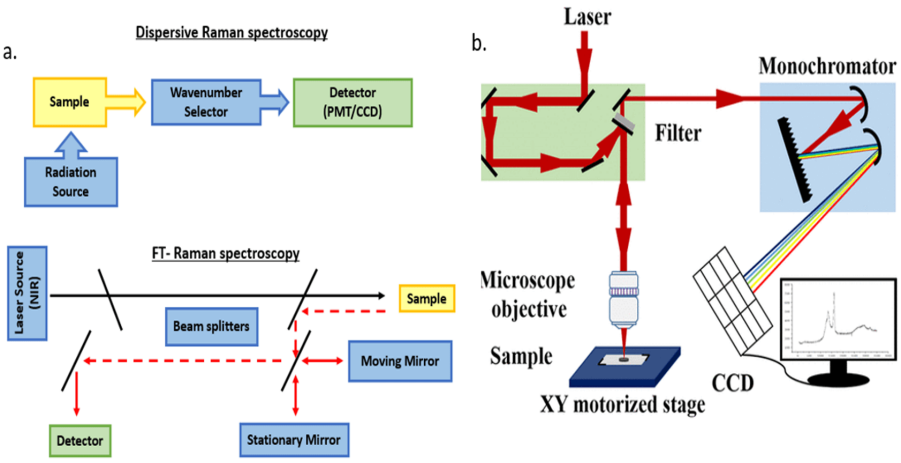


Figure 3 Instrumentational study of Raman spectrometer, a). Basic of FT Raman spectroscopy and dispersive Raman spectroscopy b). Depicting the schematic diagram of Raman spectroscopy. [22–24]

By combining Raman spectroscopy with different analytical techniques such as atomic force microscopy (AFM), scanning tunneling microscopy (STM), high-performance liquid chromatography (HPLC), and others, even trace quantities of samples can be analyzed [21]. As a result of revolutionary advances in Raman instrumentation, it is now possible to obtain spectra more easily on equipment that is less expensive and simpler to use than in the past [18, 19].

3 Discussion

3.1 Application of Raman spectroscopy in forensic science

Recent technical advances in Raman spectroscopy have led to its use in forensic science, where it has become an important analytical technique [2, 25, 26]. Raman spectroscopy has been used to analyze a variety of materials in forensic science, including drugs, fibers, explosives, medicines, colors, inorganic fillers, and other materials [27, 28]. The development of powerful Raman methods such as SERS, SERDS, and SORS has made Raman spectroscopy a valuable tool in forensic analysis [26]. Raman spectroscopy provides information about the chemical structure and identity of compounds, making it useful for forensic scientists. Raman spectroscopy is now a fully mature analytical technique on par with its counterpart, infrared spectroscopy, and is gaining recognition among forensic scientists [2].

3.1.1 Determination of cocaine and other illegal seized drug

Raman spectroscopy has been used for regular analysis in forensic toxicology because of offering rapid determination, performing nondestructive, quantification of accuracy and purity of drug without any specific reagent. So, it has become the most popular and used analytical tools to the determination of illicit drugs such as cocaine, heroines, marijuana, and other illegal drugs of abuse [29–32]. (see Figure 4)

Cocaine is usually found in two forms of chemical structure: Freebase Cocaine HCl, both have a different physical appearance like as powder (Freebase and Cocaine HCl), Paste (Freebase) and crack rocks (Freebase) [29–32].

Hydrochloride powders and Freebase are typically inhaled, while paste and rocks are typically smoked. Since it is water-soluble, the HCl form is also for used injection into arterial or venous system. As a result, deciding the form of cocaine ingested is critical for determining the propensity for addiction, as it affects the dosage consumed with drug poisoning. Furthermore,

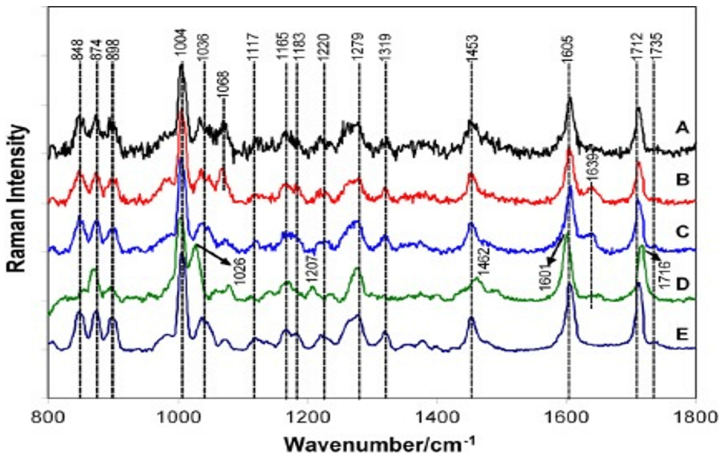


Figure 4 Raman spectrum of various forms of Cocaine A) Freebase paste in black color. B) Freebase paste in white color C) Crack rocks D) Powder form: HCl cocaine E) powder form: Freebase cocaine. [29]

the type of the drug at the time of seizure may suggest the route of traffic and the way of distribution [30, 31, 33].

Cocaine (Crack, HCl and freebase) has common Raman bands at 1605 cm^{-1} (C=C stretching); 1712 cm^{-1} (C=O stretching); 1453 cm^{-1} (asymmetric CH3 deformation); 1279 cm-^{1} (C–N stretching); 1004 cm^{-1} (symmetric stretching–aromatic ring); 898, 874, and 848 cm^{-1} (C–C stretching–tropane ring) respectively. Cocaine HCl has Raman bands with similar peak positions but lower relative amplitudes in the 898 and 848cm^{-1} wavelength ranges (tropane ring). In the HCl type spectrum, the bands at 1207 and 1026 cm-1 correspond to 1183 and 1036 cm-1 in the cocaine (freebase)spectrum, respectively. The presence of HCl causes protonated nitrogen in HCl cocaine, which affects the polarizability of the tropanic ring, resulting in spectral dissimilarities between HCl cocaine and freebase cocaine. Peaks 1735, 1319 and 1183 cm-1, which are characteristic of freebase cocaine, are absent from the spectrum of the HCl form [29–33].

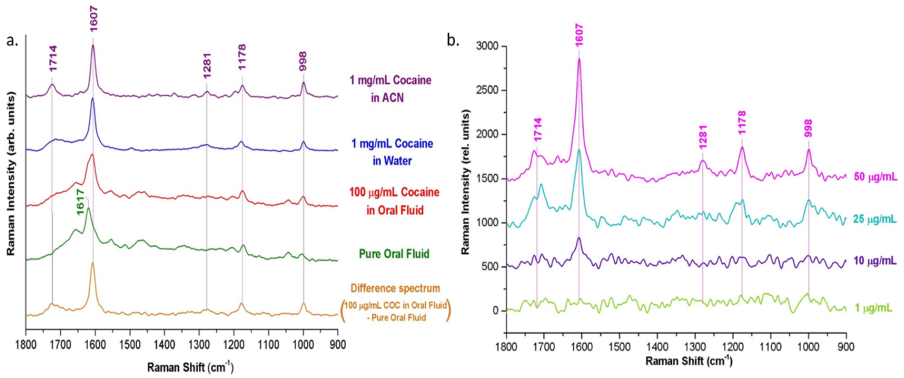


Figure 5 UV resonance Raman spectroscopy is being used to identify cocaine in oral fluid. a). Resonance Raman spectra (RR) of 1 mg/mL detection of cocaine (COC) in acetonitrile (ACN), 1 mg/mL COC in water, 100 μg/mL COC in oral fluid, pure oral fluid, and the difference spectrum between those of COC in oral fluid and the pure oral fluid b). Difference Raman spectra obtained after the subtraction of the oral fluid spectrum from the spectra of the oral fluid samples doped with COC at indicated concentrations. Excitation wavelength was 239 nm and excitation power were 10 mW. [33]

Figure 5 displays the normalized resonance Raman (RR) spectra for different samples: 1 mg/mL cocaine (COC) in acetonitrile, 1 mg/mL COC in water, pure oral fluid (OF), and an OF sample doped with 100 μg/mL of COC. The difference spectrum obtained by subtracting the spectrum of pure OF from the COC-doped OF sample is also presented.

Tentative assignments suggest the band at 998 cm^{-1} in the COC spectra corresponds to the symmetric breathing mode of the phenyl ring, while the OF spectrum shows a weak band in a similar position, potentially attributed to the phenyl ring [34]. The COC spectra feature a peak at 1607 cm^{-1} associated with the trigonal phenyl ring breathing mode and a broad band

centered at 1714 cm^{-1} corresponding to the ester carbonyl C=O stretch. Bands at 1281 cm^{-1} and 1178 cm^{-1} are assigned to C-N stretching in the amine group of COC [35]. Additionally, the OF band at 1617 cm^{-1} is possibly attributed to phenyl ring C-C stretching inside chains of proteins commonly present in the matrix [36]. Detection limit determination involved analyzing COC-doped OF samples with concentrations ranging from 50 μg/mL to 1 μg/mL. The gradual disappearance of characteristic COC bands in the difference spectra indicated a detection limit of 10 μg/mL, with no observable bands in the difference spectrum for the 1 μg/mL COC concentration [33, 36]. Raman spectroscopy is a valuable tool for collecting chemically specific information about a large variety of systems, and resonance Raman spectroscopy utilizes the frequency dependence of the polarizability to enhance the weak Raman scattering cross sections [37]. Vibrational spectroscopy such as mid-infrared (IR) and Raman spectroscopy and its fingerprinting capabilities offer rapid, high-throughput, and non-destructive analysis of metabolites in biologic samples [38]. UV-resonance Raman (UVRR) spectroscopy is an appropriate and sensitive tool to assess the chromophore structures in bleached cellulosic materials [39].

3.1.2 Detection, screening, and identification of explosives

For homeland security agencies, the detection and identification of any kind of explosive has become a major concern due to ensure the high security of any country. There are available a couple of explosive detective technologies such as X-ray scanning, ion mobility spectrometry, colorimetric tests, and dogs sniffing. Compared to them, Surface Enhanced Raman Spectroscopy (SERS) has become popular for detecting and identifying explosives due to its nondestructive properties and rapid detection capacity in various environments. SERS has undergone significant development in recent years, particularly in the detection and identification of trace levels of organic molecules, including explosives. SERS can detect and identify explosives in solution and trace levels of explosive materials [40, 41]. Gold is an excellent SERS substrate for detecting vapor explosives as it provides a specific and strong binding of a molecule to the surface. For example, cyclotrimethylenetrinitramine (RDX), TNT, and TNB can be determined with the help of SERS. Gold nanoparticles (diameter: 90–100 nm) can detect RDX at a detection level of 0.15 mg/l from a contaminated groundwater sample.

Furthermore, SERS-based explosive sensors have a broad application prospect and are being developed using nanocellulose-based substrates and aptamers. SERS technology has been reported to be able to identify target analytes quickly and non-destructively, including explosives, with high sensitivity and selectivity. Raman spectra for RDX can be observed at around 900, 1290, 1350, and 2920 cm^{-1}, while the spectra for TNT are found at 1100, 1410, 1610, and 1730 cm^{-1} [42, 43]. (see Figure 6)

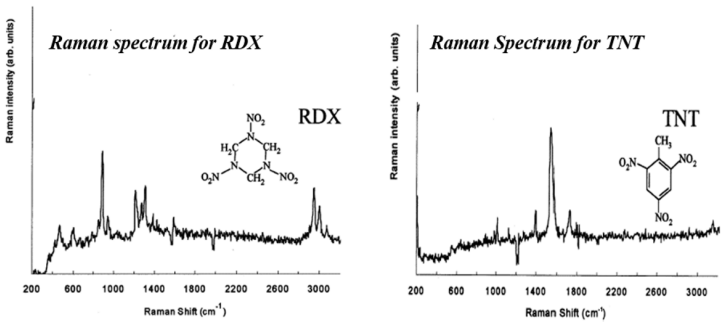


Figure 6 The determination of explosive with SERS; Raman spectrum for RDX and TNT [44, 45]

In addition, Surface Enhanced Raman Spectroscopy (SERS) has been used to identify and differentiate explosives in solution using azo dyes. These dyes have electron-donating moieties that allow for effective diazo binding and a heavy silver complexing group that attaches the product molecule to the SERS substrate, allowing for identification at nM (nanomolar) concentrations [46]. In conclusion, SERS has the ability to be a useful instrument for sampling and characterizing explosives in the environment, such as TNT, TNB perchlorate, and uranium in groundwater at low concentrations [44–46].

According to Ayoub et al. (2022), the Raman spectra of PETN, HMX, ammonium nitrate and ANFO, were measured in the range from 200 to 2000 cm^{-1} at a 1-meter distance, as depicted in Figure 7. The obtained spectra exhibited distinguishable major peaks that corresponded to the investigated substances. Subsequently, the recorded Raman spectra were compared to stored Raman spectra in the material library for matching and identification purposes. The

identification results for PETN, HMX, ammonium nitrate and ANFO demonstrated matching levels of 97.41%, 95.64%, 99.93%, 97.2%, and 98.92%. However, when conducting subsequent testing on PETN and HMX samples after a certain period, lower matching levels of 79.83% and 67.51% were obtained.

These decreased levels could potentially be attributed to factors such as impurities, sample humidity, crystallinity, and environmental conditions within the laboratory. Further research is required to thoroughly investigate the effects of sample morphology and crystallinity on Raman spectra. Nevertheless, for the present stage of the research, the system's current efficiency and its ability to identify the tested materials are considered adequate [47]. (see Figure 7)

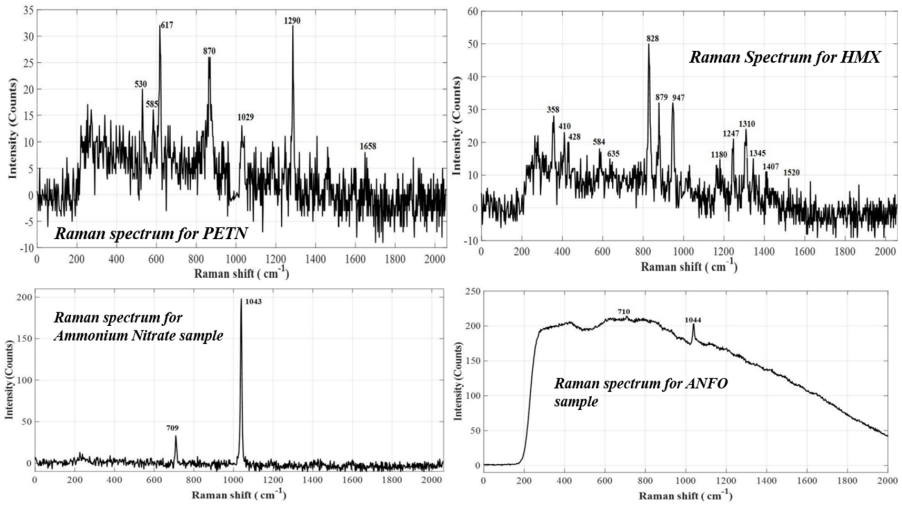


Figure 7 Raman spectrum for identifying different explosives; PETN, HMX, ANFO and ammonium nitrate sample. [47]

3.2 Application of Raman Spectroscopy in pharmaceuticals analysis

Raman spectroscopy, an immensely valuable analytical technique, holds wide-ranging applications throughout the pharmaceutical industry. Its utility encompasses the identification and analysis of diverse raw materials, including active pharmaceutical ingredients (APIs) and excipients [7,48,49]. During formulation processing, Raman spectroscopy enables in-line tests and characterization, accommodating both conventional and innovative dosage forms. Notably, it possesses the capability to detect impurities, contaminants, and counterfeiting, rendering it an indispensable tool for final quality control of formulations. This versatile analytical technique, with its unique spectral fingerprinting capabilities, contributes significantly to the advancement and integrity of pharmaceutical research and manufacturing processes [7,48–50].

3.2.1 Application of Raman Spectroscopy in drug development

The process of developing a new drug involves synthesizing the identified compound, and Raman spectroscopy has proven to be an invaluable tool for monitoring and optimizing various stages of drug synthesis. It enables the real-time assessment of reactant, intermediate, and product concentrations, as well as the determination of reaction pathways, kinetics, mechanisms, endpoints, and yields for different types of reactions [7,48,51,52]. One prominent example is the Fischer esterification, frequently employed in the synthesis of drugs like benzocaine. In this reaction, benzoic acid is esterified to produce methyl benzoate. Raman spectroscopy is adept at distinguishing the unique spectra of the reactant and product, with characteristic peaks at 780 cm^{-1} and 817 cm^{-1}, respectively [51,53]. By utilizing fiber optic coupled emersion probes and monitoring spectra every 45 seconds, the reaction rate, rate constant, and yield can be easily determined.

Additionally, optimizing reactor temperature, catalyst concentration, and type can help ascertain the activation energy, reaction endpoint, and yield optimization [51]. (see Figure 8)

Furthermore, Raman spectroscopy plays a vital role in the crystallization process, which is often the final step in drug synthesis. Crystallization separates the drug from the solvent matrix, and careful optimization is required to ensure the desired polymorph is formed. Polymorph selection is crucial as different polymorphs exhibit varying solubilities, directly impacting the drug's bioavailability and dosage. Raman spectroscopy facilitates the understanding and optimization of process conditions such as temperature, mixing rate, and concentrations, which

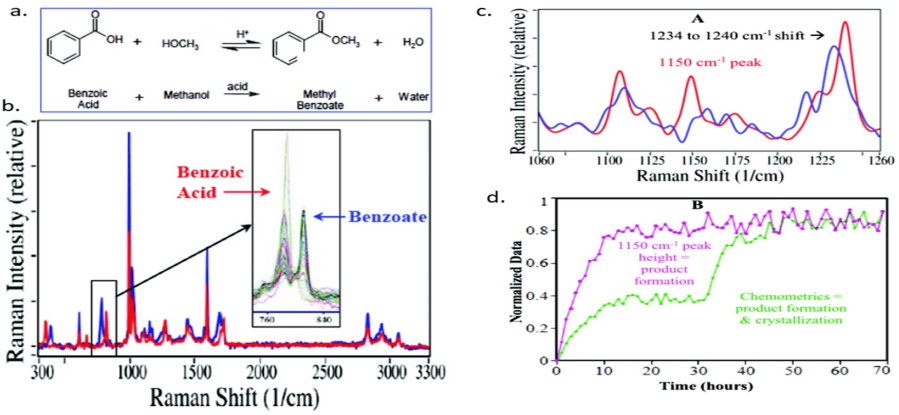


Figure 8 a) Benzoic acid esterification; b) Benzoic acid and Benzoate Raman spectra (500 mW of 1064 nm LASER irradiation). c) Raman spectra of the reactant mixture and crystalline product (500 mW LASER excitation at 1064 nm, 5-min acquisition). d) A plot of the 1150 cm-1 peak height, as well as a chemometrics correlation to both product production and crystallization. [51]

influence crystalline formation kinetics and polymorph dominance. By monitoring spectral changes and employing chemometrics models correlating these properties to the entire Raman spectrum, synthesis and crystallization processes can be accurately and precisely monitored in a single batch reactor [50, 51, 53–55].

3.2.2 Detection of counterfeit and adulterated pharmaceutical products

The rise of counterfeit prescription drugs worldwide poses a significant threat to public health and demands effective detection methods. To address this concern, the United States Food and Drug Administration (FDA) has turned to Raman spectroscopy as a powerful tool in combating counterfeit products [56]. With its ability to perform comparative analyses of both the active pharmaceutical ingredient (API) and excipients used in manufacturing, Raman spectroscopy enables qualitative identification of these components, aiding in the identification of suspected counterfeit products.

Moreover, this technique allows for the creation of unique ”spectral fingerprints” specific to genuine tablet coatings and cores, providing a robust means of distinguishing counterfeits from authentic pharmaceuticals [7,57]. The FDA’s Forensic Chemistry Centre (FCC) has leveraged the capabilities of Raman spectroscopy to scrutinize suspicious counterfeit products, highlighting its vital role in forensic investigations. Notably, Raman spectroscopy has demonstrated remarkable efficacy in detecting counterfeit drugs across diverse product types, ranging from stevia products to pharmaceutical tablets [50, 56, 58].

The Raman spectrum of an authenticated tablet core and a suspicious tablet core was compared to detect adulteration, as seen in Fig. 9(a-b). Differences in the suspect counterfeit tablet core can be seen (Figure 9a) at 400 cm-1, 1100 cm-1, and 1400 cm^{-1} [59]. In Figure 9b, a comparison is made between the Raman spectrum of a suspected counterfeit product and the Raman spectrum of the authentic active pharmaceutical ingredient (API) standard used in the genuine product. The Raman spectrum of the API standard exhibits several distinctive Raman bands. Interestingly, many of these same Raman bands can be readily observed in the Raman spectrum of the suspect counterfeit tablet core. This observation suggests a significant similarity between the Raman signatures of the suspected counterfeit product and the genuine API, indicating a potential presence of the authentic API within the counterfeit tablet core [59]. Figures 9(c-f) presents Raman spectra acquired using different excitation wavelengths and accumulation times for Viagra® samples. In the top spectrum, Raman spectra of Viagra® are obtained using a 785 nm excitation, with conditions set at 300 mW and a 10-second accumulation time, at an 8 cm^{-1} resolution. The black spectrum represents Raman spectra of Viagra® obtained using a 1064 nm excitation, with conditions set at 500 mW and a 25-minute accumulation time, also at an 8 cm^{-1} resolution. (see Figure 9)

In Figure 9d, Raman spectra of two counterfeit Viagra® samples, along with an authentic sample (bottom spectrum), are displayed. These spectra were acquired using a 1064 nm excitation, with conditions set at 500 mW and a 20-second accumulation time, at a resolution of 12-20 cm^{-1}. Figure 8e provides a photograph showing two counterfeit Viagra® tablets alongside an authentic one, visually illustrating the presence of counterfeit products in the market. Furthermore, Figure 9f depicts a Principal Component plot, demonstrating the ability to differentiate between authentic and counterfeit Viagra® samples using Raman spectroscopy.

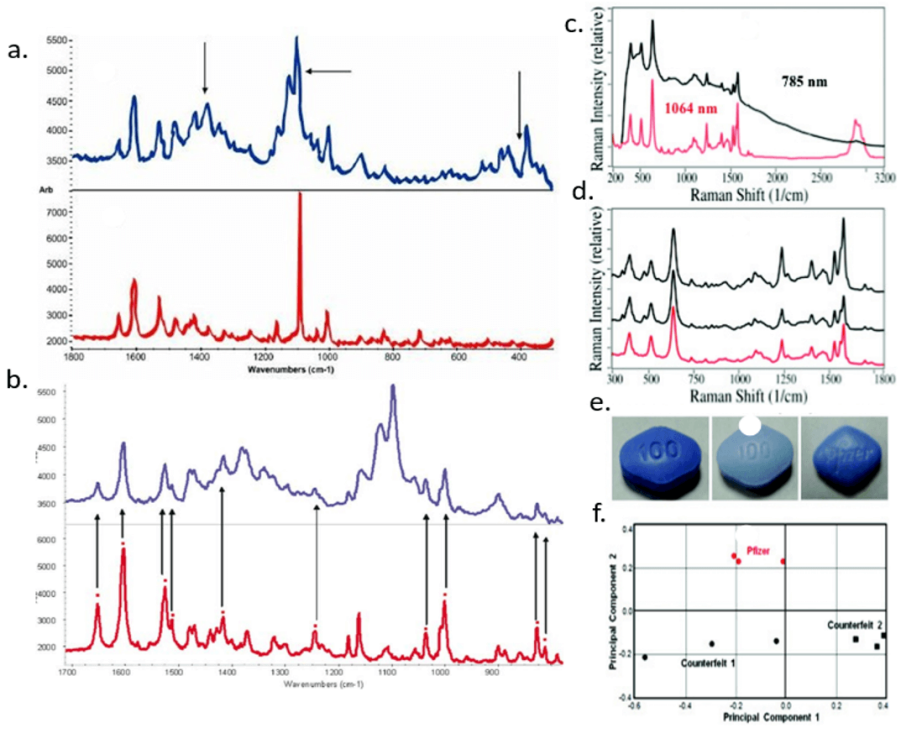


Figure 9 a). b). Raman spectrum of a suspect counterfeit tablet core(blue) and Raman spectrum of the API standard(red). Peaks used for comparison are marked with arrows. c-f). versatility and efficacy of Raman spectroscopy in the identification and differentiation of authentic and counterfeit Viagra® samples. [51,59,60]

This plot demonstrates the power of multivariate analysis techniques in distinguishing genuine products from counterfeit ones [51]. Overall, Figure 9 showcases the versatility and efficacy of Raman spectroscopy in the identification and differentiation of authentic and counterfeit Viagra® samples, offering a comprehensive approach to quality control and anti-counterfeiting measures in the pharmaceutical industry.

3.2.3 Raman Spectroscopy Screening of Excipients for the Stabilization of Amorphous Drugs

Chen et al.(2015) [6]] explored the application of high-throughput Raman spectroscopy for identifying excipients that can stabilize the amorphous form of drugs. They analyzed four model drugs (ketoprofen, danazol, griseofulvin, and probucol) in both crystalline and molten states to address the challenge of low aqueous solubility in pharmaceutical development and its impact on drug bioavailability and efficacy [61]. An aging study was conducted to evaluate the stability of amorphous drug forms over time. The results indicated variations in the excipients' ability to preserve the amorphous content during the 21-day aging test. Some excipients facilitated the conversion of drugs to crystalline phases, while others effectively maintained them in the amorphous state [61]. In this study of four model drugs (ketoprofen, danazol, griseofulvin, and probucol), all excipients enabled effective stabilization of ketoprofen in the amorphous form. Among probucol-excipient samples, one excipient favored the probucol crystalline I form, while two excipients favored stabilization of probucol almost exclusively in the crystalline II form. The remaining 13 excipients favored stabilization of amorphous probucol, and with most of these excipients, probucol was present exclusively in the amorphous form [61–64]. However, the Raman methods for danazol and griseofulvin generally predicted high crystallinity of these drugs in solid dispersions with all excipients evaluated, but further studies are needed to determine whether this is indeed the case or simply an artifact caused by the inappropriate choice of molten drugs as the Raman spectroscopy standards for their amorphous form. Many studies have investigated the stabilization of amorphous drugs, with a special emphasis on the most used excipients in stabilizing amorphous drug substances in formulations. Surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) have been widely used in stabilizing amorphous drugs [62–64].

Raman spectroscopy is an attractive analytical tool for the pharmaceutical industry, with potential applications ranging from verification of raw materials to process monitoring of drug

production to quality control of products. (see Figure 10)

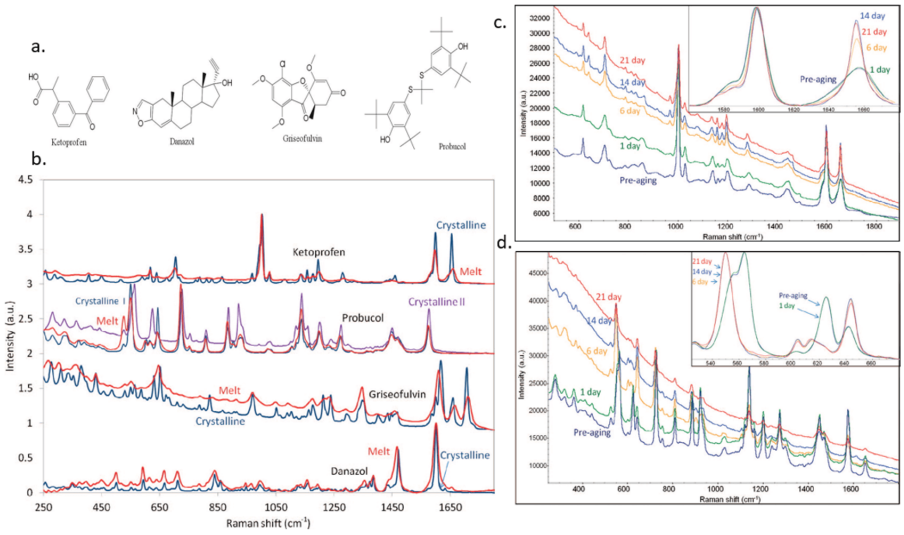
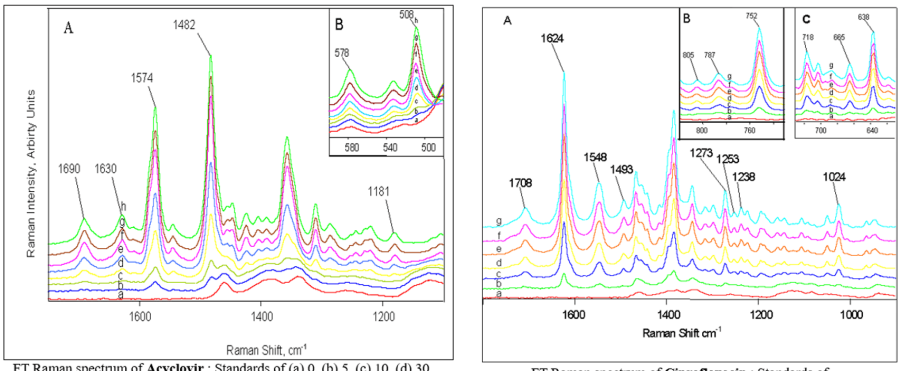


Figure 10 a). Structures of drugs selected b). Comparison of the Raman spectra of the four test drugs in crystalline and melt forms c). Spectra from the aging study of ketoprofen dispersed in PVA 13–23 K d). Spectra from the aging study of probucol dispersed in Eco surf SA7. [61]

3.2.4 Quantitative analysis of pharmaceutical dosage formulations

Raman spectroscopy has two major benefits over other spectroscopic methods: sampling simplicity and information content. Raman scattering is proportional to the concentration of the examined material, and Raman spectroscopy can be used for quantitative analysis because of this. Simple powder structures were initially quantified, but this has since been expanded to include sophisticated medication formulations such as pills, pills, microspheres, injections, and suspensions. Packaging has also been used to examine formulations. Excitation rate, sample positioning, and temperature variations are all variables in quantitative Raman spectroscopy that have a significant impact on precision and detection limit values [7, 65–67]. FT Raman spectroscopy with Univariate calibration was used to determine the quantitative concentrations of acyclovir and ciprofloxacin in pharmaceutical solid dosage formulations [68, 69]. The collected findings were in fair harmony with the National Formulary (NF 19) and the United States Pharmacopoeia (USP 24) methods. The PVC blister package was used to measure the amount of acyclovir. The bands from 1690, 1630, 1574, 1482, 1181, 578, and 508 cm^{-1} were used in this experiment. For band amplitude and band area measurements, calibration curves were found to be linear, with correlation coefficients of 0.997-0.9993 and 0.996-0.9991, respectively [69]. (see Figure 11)



FT Raman spectrum of **Acyclovir** : Standards of (a) 0, (b) 5, (c) 10, (d) 30, (e) 50, (f) 70, (g) 90 and (h) 100 % w/w

FT Raman spectrum of **Ciprofloxacin** : Standards of (a) 0, (b) 10, (c) 30, (d) 50, (e) 70, (f) 90 and (g) 100 % w/w

Figure 11 Acyclovir and Ciprofloxacin determination by solid state FT-Raman spectroscopy. [68, 69]

In the case of ciprofloxacin, the bands detected in 1708, 1624, 1548, 1493, 1273, 1253, 1238, 1024, 805, 787, 752, 718, 665, and 638 cm^{-1} were used, and the calibration curves obtained were linear in the concentration range of 3-100 percent w/w, with correlation coefficients of

0.99-0.996 for band amplitude and 0.991-0.9993 for band area measurements [68]. Overall, the reproducibility of certain parameters, such as particle size, sample packing density, and mixture homogeneity, determines the accuracy of quantitative Raman analysis of solid powder mixtures.

4 Evaluation of Raman Spectroscopy in comparison to other techniques

Raman spectroscopy has emerged as a prominent analytical technique, primarily due to its operational simplicity and minimal sample preparation requirements. The fundamental principle involves the irradiation of samples with laser light, followed by the collection and analysis of the resulting scattered light. This distinctive feature eliminates the need for extensive sample cleanup procedures and facilitates rapid analysis. Furthermore, Raman spectroscopy is non-destructive, enabling the preservation of valuable and limited sample quantities, which is particularly advantageous when studying expensive materials. Additionally, this technique allows for the examination of samples enclosed within various matrices such as paper, plastic, glass, and ceramics, obviating the need for bulk sampling and minimizing the risk of unintended contamination [7, 65–67].

Another noteworthy advantage of Raman spectroscopy is its insensitivity to water interference, rendering it suitable for the analysis of aqueous solutions. Unlike certain other analytical methods, Raman spectroscopy does not necessitate instrument purging to mitigate the influence of atmospheric humidity. Furthermore, the exceptional discriminatory power of Raman spectroscopy stems from the fact that each molecule possesses a unique Raman spectrum, making it a valuable tool for both qualitative and quantitative investigations [8, 70, 71].

4.1 Comparative Analysis of Analytical Techniques for Forensic Science and Pharmaceuticals: A Focus on Raman Spectroscopy

The comparative advantages and limitations of Raman spectroscopy in contrast to other widely used analytical techniques, such as FT-IR and LC/GC-MS, in the fields of forensic science and pharmaceuticals.

4.1.1 Raman spectroscopy

Raman Advantages: Raman spectroscopy stands out for its non-destructive nature, allowing samples to be examined without altering their composition [72]. This is particularly valuable in forensic science and pharmaceuticals, where sample preservation is crucial for accurate analysis. Raman's molecular specificity is another highlight. It furnishes detailed information about molecular vibrations and chemical bonds, aiding in precise identification of compounds and polymorphs [73]. Furthermore, Raman is adept at analyzing aqueous solutions, a common feature in both fields, as water does not hinder the technique's effectiveness [74]. Additionally, Raman requires only minimal sample quantities, which is an advantage when working with limited or precious samples [7, 75].

Raman Limitations: However, Raman spectroscopy faces certain limitations. Fluorescence interference can pose a challenge, leading to inaccuracies in results due to overlapping signals. This drawback might necessitate additional sample treatment or techniques to mitigate fluorescence effects [72, 76]. Raman's penetration depth is confined to surface analysis, restricting its utility for samples with significant bulk or depth [77]. Moreover, Raman signals are inherently weaker than those from some other techniques, potentially limiting its sensitivity in detecting compounds present in low concentrations [78].

4.1.2 FT-IR

FT-IR Advantages*:* In comparison, Fourier-transform infrared spectroscopy (FT-IR) presents its own set of advantages. Its versatility allows analysis of various sample forms, including solids, liquids, and gases, making it adaptable to a wide array of samples encountered in forensic and pharmaceutical contexts [79]. The rapidity of FT-IR analysis is noteworthy, delivering results within minutes, which is beneficial for high-throughput scenarios [80]. Furthermore, FT-IR can facilitate quantitative analysis by measuring absorbance intensities, aiding in accurate compound quantification [81].

FT-IR Limitations: Nevertheless, FT-IR has limitations worth considering. Sample preparation can be demanding, especially for solid samples, potentially influencing their integrity and introducing a degree of variability [82]. The presence of water absorption bands can complicate the analysis of aqueous samples, a common scenario in both forensic science and pharmaceuticals. While FT-IR provides information about functional groups, it may not offer

the same level of molecular specificity as Raman spectroscopy [83].

4.1.3 LC/GC-MS

LC/GC-MS Advantages*:* Liquid chromatography/gas chromatography coupled with mass spectrometry (LC/GC-MS) offers its own unique strengths. Its high sensitivity is particularly advantageous when detecting trace-level compounds, a common requirement in both forensic science and pharmaceutical analysis [84]. The technique's capacity to analyze a broad range of compounds, from small molecules to complex biomolecules, is relevant in diverse applications within these fields [85, 86].

LC/GC-MS Limitations: However, LC/GC-MS has its own set of limitations. Sample complexity necessitates intricate sample preparation and separation procedures, potentially compromising the sample's integrity and introducing variability. Additionally, the ionization process used in mass spectrometry can be destructive, altering the sample and leading to concerns about accurate representation. Furthermore, LC/GC-MS typically necessitates prior knowledge of the compounds of interest, limiting its application when dealing with unknown or unexpected substances [84].

The choice of analytical technique in forensic science and pharmaceuticals should align with the specific analytical requirements and limitations of each method. Raman spectroscopy's strengths in non-destructive analysis, molecular specificity, compatibility with aqueous samples, and minimal sample requirements make it a valuable tool in certain scenarios. By considering these comparative advantages and limitations, researchers and analysts can effectively harness the potential of Raman spectroscopy while understanding its constraints in specific circumstances.

5 Conclusion

Raman spectroscopy is a powerful and excellent analytical tool for investigating and analyzing different kinds of samples in both forensic and pharmaceutical fields. Its significance as a quantitative instrumental technique is strengthened by its nondestructive and fast analysis capability, ease of operation, sampling simplicity, and broad applicability in aqueous media. In forensic science, this non-destructive vibrational technique can identify drug substance abuse quickly, preserving evidence retrieved from the crime scene and allowing for further examination of the sample. It is an economical tool that can quantify and identify all kinds of drugs, including cocaine, without producing any chemical waste that helps to prevent contamination of the environment. Additionally, it has become a popular scanning tool in airports, public areas, customs departments, and post offices to detect any kind of explosive, including RDX, TNT, TNB, HXA, and other drugs. In the pharmaceutical industry, Raman spectroscopy is a noninvasive and non-time-consuming tool that can detect and quantify various APIs and doses from solid tablets, capsules, and other pharmaceutical products while monitoring and controlling quality and adulteration of different stages of drug production. Although Raman spectroscopy has some limitations, the recent advancements of technology, such as sampling conditions, a large number of laser wavelengths, and data collection tools, have helped make it a cost-effective analytical technique in the forensic and pharmaceuticals industry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to express our sincere appreciation and gratitude to the University of Tennessee, Knoxville, USA and the Institute of Radiation and Polymer Technology, Bangladesh Atomic Energy Commission, Dhaka, Bangladesh for their invaluable resources and unwavering support throughout the course of this research.

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