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Review Article

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Comparative Evaluation of Conventional Backscattered Raman Spectroscopy and Transmission Raman Spectroscopy (TRS) for Monitoring Authenticity of APIs in Fixed Dose Combination Drug of Ibuprofen and Paracetamol

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Abstract Raman spectroscopy, one of the most widely used optical spectroscopic technique can provide molecular information about pharmaceutical drugs. This particular spectroscopic technique has proven its potential over the others by overcoming the barriers faced in traditional approaches and by providing unique benefit of molecular characterization in near real time. In this spectroscopy method, incident light interacts with the molecule inelastically and the scattered light has specific vibration modes of molecules in form of sharper Raman peaks. The technique thus can identify the molecular structure of the given tablet sample. Since the sample used for Raman measurements can be reused, it can provide a non-destructive way of analyzing. There are two different configurations of Raman spectroscopy: (1) back-scattered and (2) transmission. In back-scattered Raman spectroscopy, tablet is illuminated using a laser source and the Raman's back-scattered from the tablet surface is collected for the detection. In contrast, transmission Raman spectroscopy (TRS) collects Raman signals transmitted through the tablet sample. While back-scattered Raman signal is only originated from the superficial depths though with excellent signal to noise ratio (SNR), transmission Raman signal can be obtained through the whole tablet, however with lower SNR. This report presents the results of the Raman spectral measurements of binary NSAID drug, paracetamol-ibuprofen using both the configurations of Raman spectroscopy. Both the configurations could reveal identical signatures. Owing to better SNR, back-scattered Raman spectroscopy is suggested as a potential tool for API determination of binary NSAID paracetamol-ibuprofen drug.

Keywords Paracetamol Tablet, Ibuprofen Tablet. Transmission Raman spectroscopy, Back scattered Raman spectroscopy

Introduction

Health is the need of everyone in society. With the increasing healthcare services worldwide, the pharmaceutical industry has succeeded in producing drugs and medicines that improve the quality of life. The quality of life and life expectancy of many patients has been improved by medicine [1]. Medications can treat it, reduce symptoms, delay the onset of the disease, and prevent complications. They usually offer good value for money.

NSAIDs block the production of chemicals in the body that cause pain. NSAIDs are effective in treating pain caused by tissue damage, such as arthritis. NSAIDs are also great for back pain, colds, and headaches [2] Used as an

analgesic and antipyretic, and nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory and pain-relieving properties.

There are many methods used in the pharmaceutical industry. Infrared spectroscopy collects information at all frequencies simultaneously in one second. Therefore, IR can be used to identify less powerful objects and make a scan before starting the explosion. However, it contains negative molecular units with small oscillating dipoles during vibrational transitions because these species do not absorb infrared well. FTIR stands for Fourier Transform Infrared Spectroscopy and is a sensitive and fast method to obtain good spectra. The benefits of upgrading from existing diffuse infrared equipment to FTIR will be immediately apparent in terms of quality, data collection speed, data reproducibility, and ease of maintenance and use. FTIR devices have only one beam, while scattering instruments usually have two beams.

Identification and identification of ibuprofen and paracetamol in methods such as Raman spectroscopy, similar to infrared spectroscopy, is the umbrella of vibrational spectroscopy techniques often used to study molecular vibrational structures and identify molecular fingerprints. Quantitative analysis of

chemical compounds was routinely done by HPLC. However, this process takes a long time and destroys the model. In many applications, it will be useful to replace it with a different visual method that is fast, non-destructive and non-invasive. But HPLC can be an expensive concept, requiring countless expensive electronics, manpower, and extensive support. Researching problems or creating new systems can be messy. Raman spectroscopy has many applications in the pharmaceutical industry, such as the quantitative determination of active pharmaceutical ingredients and the classification of active ingredients in tablets by Raman imaging. Recently, Raman spectroscopy has been successfully used to assess the quality of drugs and detect counterfeit drugs such as Viagra or Cialis tablets, Lipitor tablets and others. Along with these advances and the use of Raman spectroscopy has been the development of handheld Raman spectrometers. Portable Raman equipment is cheaper and cheaper than conventional Raman spectrometers.

Current research: First, use a method based on Raman spectroscopy in NSAID pharmacies to determine whether the label contains ibuprofen, paracetamol, or a mixture thereof, and second, establish benchmarks to determine the amount of money in it. pharmaceutical formulations APIs are available.

On the other side, poor-quality pharmaceutical items can affect customers' health or result in a number of illnesses [6], [7]. Unfortunately, chemical changes in pharmaceutical formulations can happen as a result of exogenous influences, such as illegal medication counterfeiting for use by the general public and chemical instability of APIs caused by interactions between APIs and excipients under less-than-ideal circumstances. The latter, for instance, may result from the degradation of the packing system (such as tablets or capsules) as a result of unfavourable climatic conditions during shipping, storage, and use, especially in tropical areas [3].

Raman Spectroscopy

Raman spectroscopy is a molecular spectroscopic technique that utilizes the interaction of light with matter to gain insight into a material's make up or characteristics, like FTIR. The information provided by Raman spectroscopy results from a light dispersion process, whereas IR spectroscopy relies on absorption of light. Raman spectroscopy yields information about intra- and inter-molecular vibrations and can provide additional understanding about a reaction. Both Raman and FTIR spectroscopy provide a spectrum characteristic of the specific vibrations of a molecule ("molecular fingerprint') and are valuable for identifying a substance. However, Raman spectroscopy can give additional information about lower frequency modes, and vibrations that give insight into crystal lattice and molecular backbone structure.

Inline Raman spectroscopy is used to monitor crystallization processes and reveal reaction mechanisms and kinetics. Combined with analysis tools, this data enables informed reaction understanding and optimization.

Since its inception many years ago, Raman spectroscopy has paved the way for understanding materials, particularly carbonaceous materials such as graphite. Currently, Raman analysis has gone beyond the scientific laboratory to have industrial applications in areas such as food and pharmaceutical manufacturing, environmental protection, and textiles.

Technology was developed simultaneously in the early 20th century by two different scientists unaware of each other's findings. Chandrasekhara Venkata Raman won the Nobel Prize for his efforts, and both phenomena and technologies based on his observations are named after him. But Grigorij Samuilovič himself got to the same point as Raman, and around the same time. Raman spectroscopy as an analytical method was widely developed in the second half of the 20th century, when spectrometers equipped with lasers were first developed for research purposes.

Like all spectroscopic methods, Raman spectroscopy is based on the interaction of radiation and matter. Absorption, conduction, and scattering are phenomena that control the interaction of energy and matter.

The difference between the incoming and outgoing electron photon is called the Raman shift. Raman spectroscopy uses laser light on a sample to create this effect, and then Raman spectrometry uses special sensors to record the results. A human or computer analyzer analyzes the Raman data from the spectrometer to reveal various elements of interest in the sample.

Background

The Raman spectroscopy is further used in radiation in scattering of visible light. It is a defined for chemical structure in spectrum which differentiate is called Raman spectrum. They are used to determine the vibration modes of molecules. The photons are incident of particles of inelastic scattering process is also called Raman Scattering. The source of monochromatic light is usually in lased of visible λ rays, x- ray, NIR, NUV range is used. The resulting energy of Raman spectrum of lass photons being in given information is transmitted to photons. Raman spectroscopy is the measurement of wavelength and intensity of in elastically scattered light from molecules. When the incident photon interacts with the molecule, the energy is either gained or lost. That is, here a small fraction of light, approximately 1 in 107 photons is scattered at optical frequencies different from, usually lower than the frequency of incident photons, called inelastic scattering. This inelastic scattering is called Raman scattering, which can occur with a change in vibrational, rotational or electronic energy of a molecule. If the scattering is elastic, the process is called Rayleigh scattering.

Raman effect

Raman spectroscopy is based on the well-known Raman effect in which light falling on the Sample interacts with it inelastically. During the course of interaction, light gets scattered and Scattered light in generally has the energy same to the energy of the incident light. This is known as Rayleigh scattering or elastically scattering. However, very few photons may get inelastically Scattered by virtue of change in the energy [15]. This inelastic scattering is called RamanSc which can occur with a change in rotational, vibrational, or electronic energy of a Molecule. Raman scattering is of two types: Stokes and anti-Stokes. Further, according to Maxwell Boltzmann distribution,

$$N2 = N1Exp(-Hc/kT)$$

The intensity of Raman transition line not only depends upon transition probability but also Depends on the population of initial state. Since the origin of anti-Stokes lines is from higher Vibrational state and the population is low in this state as compared to the ground vibrational State, so the intensity of anti-Stokes transition line is weaker than the Stokes transition line.

Classical theory of Raman scattering

In the classical theory of Raman scattering, the molecule is considered as an oscillatin scatterin and the changing dipole moment give rise to polarizability. So a molecule to be Raman active, Rate of change of polarizability ($\partial\alpha/\partial q$) with vibration molecules must not be equal to zero. However, this theory of Raman effect fails to explain the reason why anti-Stokes lines are weaker.

Quantum theory of Raman scattering

In this theory of Raman scattering, energy level of the sample or interacting molecules areI and based on the transition to virtual state, Raman scattering is explained. If energies of the ground state, Ea and returning state, Eb

are same, there is no change in the frequency of Scattered light. There is no gain or loss of energy in photon, only the direction of the photon changes. This is known as elastic collision and this type of scattering is known as Rayleigh scattering. If Ea > Eb, i.e. frequency of scattered photon is more than that of the incident photon. It means that the molecule is already in the excited state and gives some of its energy to the incident photon thus gains energy. This is known as inelastic collision, and this type of inelastic collision is known as anti- Stokes Raman scattering. If Ea < Eb, then frequency of scattered photon is less than that of the incident photon. It means that the molecule has absorbed some energy and scattered photon has come to the lowest ground energy level having low energy. This type of scattering is known as Stokes Raman scattering.

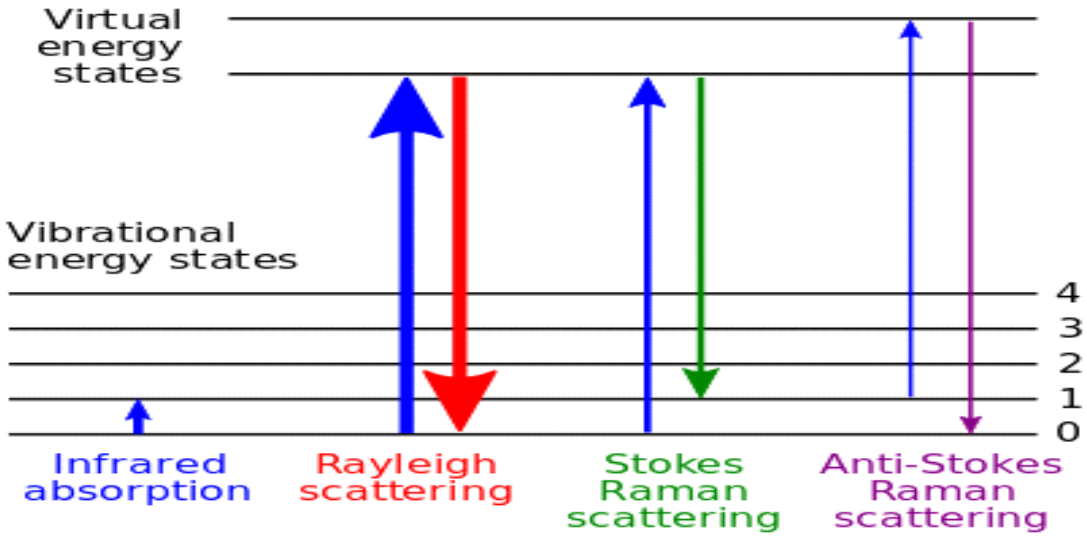

Figure 1: Spectrum

Basic Raman set up

A basic experiment setup of Raman spectroscopy has following major subparts: a laser source for Illumination, an optical fiber to deliver the laser light, and a Raman spectrograph equipped with a Charge couple device (CCD) to measure the spectra [15]. An example of such a system is shown

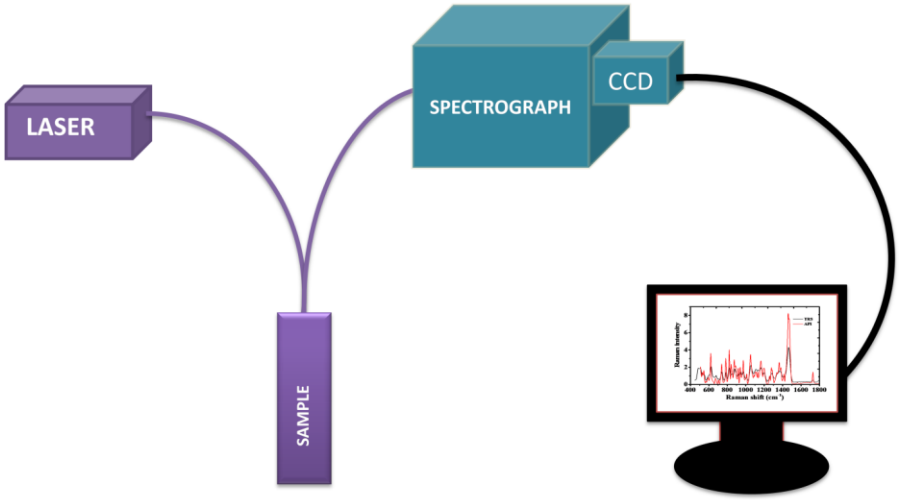

Figure 2: Schematic of basic Raman setup Generally, two different configurations of Raman spectroscopy are used: (a) Backscattered Raman spectroscopy and (b) Transmission Raman spectroscopy

Backscattered Raman spectroscopy

Back-scattered Raman spectroscopy is one of the traditional configurations of Raman Spectroscopy in which illumination and collection of Raman signal is done from the same side of the tablet sample. In the figure displayed below, 785 nm diode laser is used for excitation. The Light is spectrally purified and then steered towards the sample using a dichroic mirror and an Objective lens. The Raman signal backscattered from the sample surface is collected by the same Objective lens. This light is passed through the dichroic mirror and using a notch filter elastically Scattered component of it is removed. The light is then focused on a Raman spectrograph Equipped with a CCD detector.

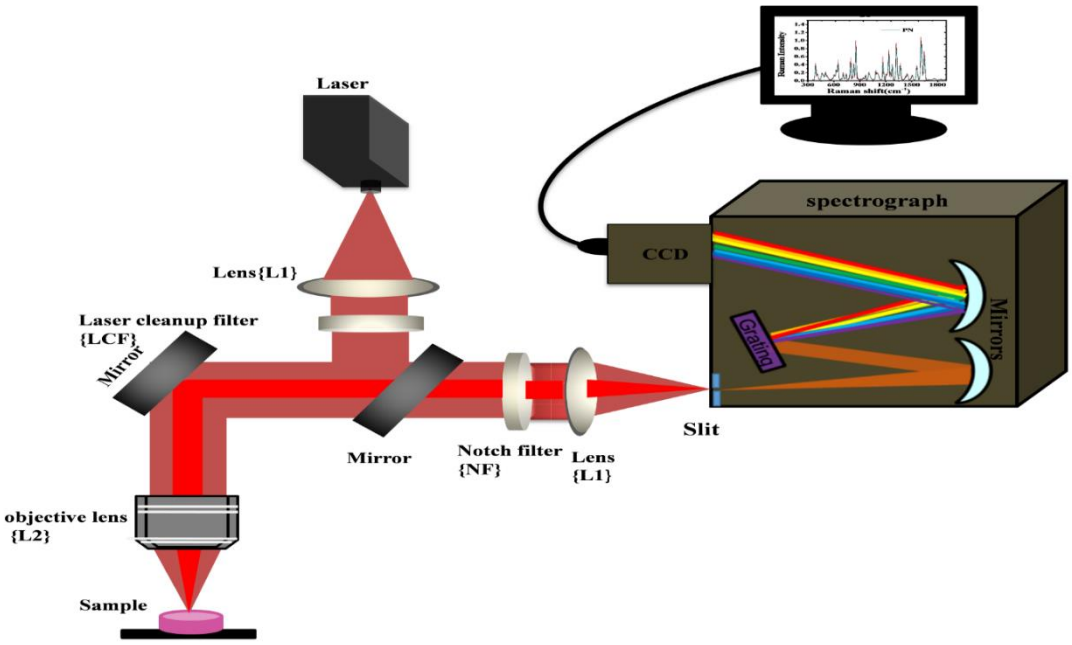

Figure 3

Transmission Raman spectroscopy

Transmission Raman spectroscopy (TRS) is a modern variant of Raman spectroscopy which has advantage of deep probing of bulk content of diffusely scattering samples like pharmaceutical tablets. In this system, the light source used was a multi-mode diode laser (CL-2000, Crystal Laser) with central wavelength of 785 nm. The light produced from the laser source was first collimated using a lens. The laser beam was then spectrally purified using a laser clean up filter. Then the beam was focused onto the sample using another lens. An additional lens placed opposite side of the sample collects the scattered light and the transmitted Raman photons get passed through a notch filter which eliminates the elastically scattered Rayleigh component. The

purified Raman beam is then focused onto tip of a multimode fibre using a lens. The fiber delivers the light collected into a spectrograph. The spectrograph is equipped with a thermo electrically cooled CCD detector. The measured TRS signal is displayed in a desktop PC.

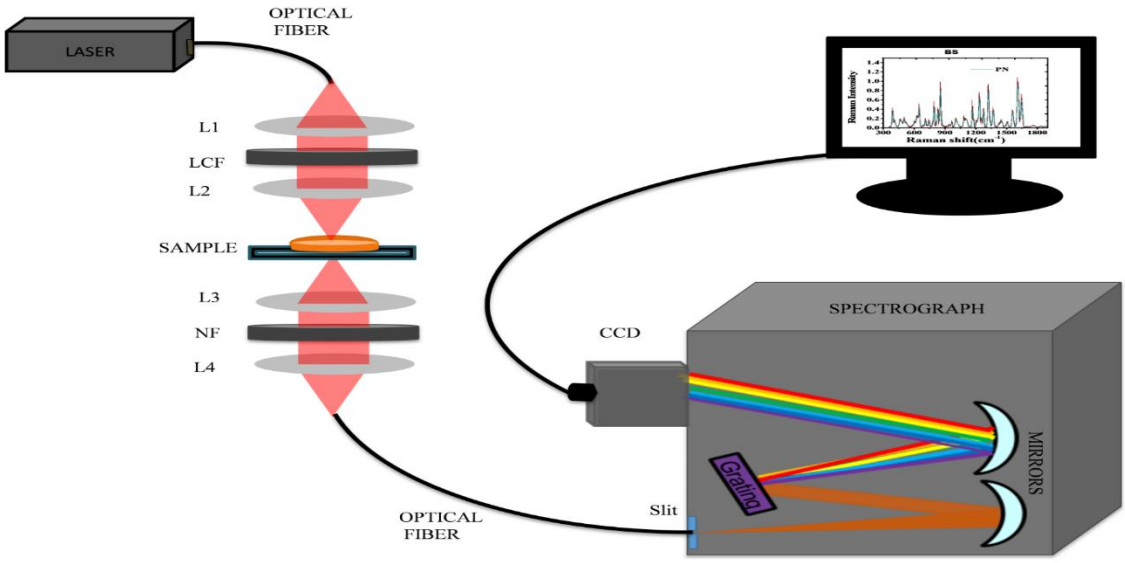

Figure 4

Application of Raman Spectroscopy

- Raman spectroscopy has been developed as a versatile and powerful technique with applications in information science, biology, medicine, industry and even the rest of the world.
- The most advanced application of Raman spectroscopy is the characterization of carbon materials, a process that has led to many discoveries in materials science over the past century.
- Advanced carbonaceous materials such as carbon nanotubes (CNTs), graphene and amorphous carbon are now measured and studied by Raman spectroscopy.
- Raman spectroscopy is also used in the study of metal, ceramic and polymer nanoparticles. These materials will reveal interesting properties for chemical applications, including biocompatibility, magnetism, and photoluminescence. Tagging them with Raman spectroscopy reveals these features by investigating how they interact with their biological environment.

Basic principles of Raman Spectroscopy

When light interacts with molecules in a gas, liquid, or solid, the vast majority of the photons are dispersed at the same energy as the incident photons. This is described as elastic or Rayleigh scattering. A small number of these photons, approximately 1 photon in 10 million will disperse at a different frequency than the incident photon. This process is called inelastic scattering, or the Raman effect, named after Sir C.V. Raman who discovered this and was awarded the 1930 Nobel Prize in Physics for his work. Since that time, Raman has been utilized for a vast array of applications from medical diagnostics to material science and reaction analysis. Raman allows the user to collect the vibrational signature of a molecule, giving insight into how it is put together, as well as how it interacts with other molecules around

A scattering technique is Raman spectroscopy. Its foundation is the Raman Effect, which states that a small portion of dispersed radiation has a frequency that differs from that of monochromatic incident light. It is predicated on how incident radiation interacts with vibrating molecules to scatter inelastically. It examines the vibrations of molecules. A monochromatic laser beam is used in Raman spectroscopy to illuminate the sample, which interacts with the sample's molecules to produce scattered light. A Raman spectrum is created using scattered light that has a different frequency than the incident light (inelastic scattering). Raman spectra are produced by inelastic collisions of the sample's molecules with incident monochromatic light.After interacting with the sample's molecules,

monochromatic radiation that hits the sample scatters in all directions. Rayleigh scattering is the process by which a significant portion of this dispersed radiation has a frequency equal to that of the incident radiation. Raman scattering only occurs when a very small portion of the scattered radiation has a frequency that is different from the incident radiation's frequency. Stokes lines can be seen in the Raman spectrum when the frequency of incident radiation is higher than the frequency of scattered radiation. Anti-Stokes lines, however, show up in the Raman spectrum when the frequency of incident radiation is lower than the frequency of scattered radiation. The normal measurement angle for scattered radiation is a right angle to the radiation incident.

Stokes altered Stokes bands are more intense than anti-Stokes bands because Raman bands entail transitions from lower to higher energy vibrational levels; as a result, they are detected in traditional Raman spectroscopy.Since fluorescence interferes with Stokes bands, anti-Stokes bands are measured with fluorescing samples, and instead. The wavelength of the incident radiation has no effect on the size of Raman shifts. The wavelength of the light that is incident affects Raman scattering.

Raman spectra are expressed as wavelength versus intensity. Raman spectra can be detected between 4000 and 10 cm (10). However, Raman-active normal vibrational modes of organic molecules occur between 400 and 400 cm1. Raman spectroscopy generally covers the wavenumber range of 400-5 cm1 to 4000-3800 cm1 depending on the architecture and optical components of the spectrophotometer. Raman spectra differ from their infrared (IR) counterparts due to the combination, and difference bands are less common in Raman implication. Both dispersive and non-dispersive Raman spectrophotometers are possible. The dispersive, non-dispersive Raman spectrophotometers use prisms or gratings. An interferometer like the Michelson interferometer in the Fourier Raman Spectrophotometer Transformed Raman Spectrometer. The

can isolate individual channels using a bandpass filter. In dispersive devices, a notch filter is often used in conjunction with a high-quality grating monochromator. Techniques such as double or triple grating monochromators, super filters, reject filters, holographic notch or edge filters, and holographic filters are used to separate Rayleigh scattering from weak Raman lines. Early versions of dispersive Raman spectrophotometers used photomultiplier tubes and thermoelectrically cooled photodiode array detectors. 3 Due to advances in measurement and technology, these devices have been replaced by more compact digital devices (CTDs) such as charge-coupled devices (CCDs) and drug reactions (CIDs). These components are used in arrays and used as detectors.

Conclusion

To conclude, we have measured and analyzed Raman signals of seven different brands of paracetamol-ibuprofen tablets using back-scattered and transmission configurations. It was found that back-scattered Rama signal does not deviate significantly from the Raman signal of API. So, it was inferred that back-scattered configuration is applicable for API determination of uncoated tablets including the given samples. Although TRS too could all the characteristics of the tablet, owing to its reduced SNR, the preference is given to back-scattered configuration for the uncoated tablets. This preliminary investigation suggests that Raman spectroscopy has great potential for API determination of uncoated tablets and can be used in near future for inline API monitoring of various pharmaceutical products including the present drug.

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