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Raman Spectroscopy: A Review

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Abstract This article reviews recent advances in Raman spectroscopy its types and its applications, from the perspective of pharmaceutical analysis. The emerging concepts enable rapid non-invasive analysis of pharmaceutical formulations and could lead to many important applications in pharmaceutical settings, including quantitative bulk analysis of intact pharmaceutical tablets in quality and process control. Raman spectroscopy is particularly useful as a screening tool for quick evaluation of chemicals and pharmaceuticals since it is simple, non- destructive and information-rich.

Keywords Raman spectroscopy, non- destructive

Introduction

The pharmaceutical industry has become a very important part of our day to day lives, it not only discovers but also develops and market pharmaceutical drugs for use as medications [1-2]. Pharmaceuticals have been used to treat diseases for thousands of years earlier. Industries have brought medications for many life-threatening diseases like diabetes, cancer, leprosy, hypertension, tuberculosis, meningitis, malaria etc. One of the most practical and popular ways to deliver medications is through the use of tablets. But in recent years, public's health has seen a significant problem with counterfeit pharmaceutical items. All countries throughout the world are affected by the growing problem of counterfeit medicines, which makes up 10% of the global market. Any class of medications can have it [3]. However, it usually occurs in drugs used to maintain a healthy lifestyle in developed nations and in drugs used to save lives in developing nations. An issue with the active pharmaceutical ingredient (API) or excipients of a counterfeit medicine is possible. As a result, it may range from having no active pharmaceutical ingredient to having an insufficient amount of (API), or even a lethal product [4].

A variety of methods for example, titrations [5], chromatography [6], gravimetric analysis [7], electrophoretic methods [8], nuclear magnetic resonance (NMR) [9] etc. have been proposed to characterize and analyze the tablets. However, these techniques are time consuming, require sample preprocessing, expensive and the tested sample cannot be re-used. To overcome these limitations, spectroscopy-based techniques have been proposed and adopted in recent years. These include UV spectrophotometry [10], FTIR [11], NIR [12] & Raman spectroscopy [13].

To overcome such problems, use of Raman spectroscopy is recommended. To start with, based on the wavelength and intrinsic properties, light can interact with matter in a many different ways: it can be absorbed, transmitted, reflected, refracted, diffracted or scattered [14]. Spectroscopy is the study of the interaction between light and matter, it examines and measures how light or other radiation is absorbed and emitted by materials. The major focus of spectroscopy is the dispersion of light and other radiations created by an item, which enables the investigation of variety of its features. The ability to determine the composition, physical structure and electronic structure of different particles at the molecular or atomic level has led to extensive use of spectroscopy.

Raman spectroscopy, which is based on the inelastic scattering of light by molecules, is a method for non-destructively testing and identifying the molecular structure of the material. This method can offer comprehensive details regarding the molecular interactions, polymorphism, crystallinity and chemical structure of a substance [15]. Chandra shekhar Venkata Raman and Krishnan made the initial discovery of the effect in 1928[16], for which C. V. Raman was awarded the 1930 Nobel Prize in Physics. Raman spectroscopy was first utilized in physics and chemistry [17] and was primarily employed to research the vibrations and structure of molecules [18-19], even though it is now used in biology and medicine.

Raman Effect and Raman Spectroscopy

Raman spectroscopy technique measures intensity of in elastically scattered light as a function of wavelength. 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 10^7 photons is scattered at wavelengths different from, usually higher than the wavelength 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. In case of same wavelength or same energy, the process is called Rayleigh scattering [2].

When monochromatic light is irradiated on a tablet, it interacts with the sample via reflection, absorption or scattering. After getting the absorption of the incident light, molecule goes into higher vibration state and returns back to the ground state. In this process, most of the light is elastically scattered i.e. Rayleigh scattering and a little portion is in elastically scattered i.e. Raman scattering (composed of Stokes and Anti-stokes portions). It is the scattering of the radiation that happens and delivers information about molecular structure. This in elastically scattered portion contains the knowledge which we have an interest in. The intensity of 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.

Scattering occurs when photons of light interact with the molecules of a substance. A majority of photons collide with molecules and have no change in their energy after collision. This is referred to as Rayleigh scattering. However, few photons collide with molecule and exchange energy with them (inelastic scattering) this is referred to as Raman scattering, it can be stokes or anti stokes. The change in energy of molecule after collision can be described on the basis of the law of conservation of energy.

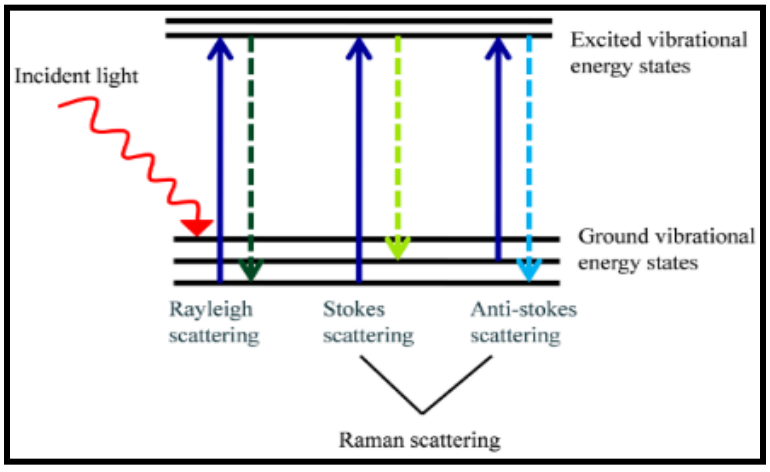

Figure 1: Energy level diagram to show the quantum mechanical theory of Raman effect

Types of Raman Spectroscopy

There are a number of advanced types of Raman spectroscopy, including surface-enhanced Raman, resonance Raman, stimulated Raman, transmission Raman and spatially offset Raman.

1. Surface-enhanced Raman spectroscopy (SERS)

Generally performed using a silver or gold colloid or a substrate containing silver or gold. Surface plasmons of silver and gold are irradiated by laser, resulting in an increase in the electric fields around the metal. Given that Raman intensities are proportional to the electric field, there is a huge increase in the measured signal [20]. Initially SERS was used for measuring low-concentration solutions, with single molecule detection sensitivity demonstrated in 1997 [21-22]. However, the first intrinsic SERS experiments of cells were demonstrated later by Kneipp et al. using 60 nm AuNPs with 830 nm excitation, requiring only 3-5 mW to obtain spectra with 1 second integration times, resulting in faster low-power imaging [23-24]. SERS probes can also be used as sensors for measuring other properties of cells, such as their pH, [25].

2. Resonance Raman spectroscopy

Resonance Raman only amplifies Raman scattering from a specific vibrational mode of the molecule in resonance with the excitation illumination. Other modes and molecules in the sample are not affected. A suitable target molecule for resonance Raman spectroscopy must have strong Raman-active bands as well as absorption bands at practical wavelengths [26]. The excitation wavelength is resembling to an electronic transition of the molecule or crystal, so that vibrational modes associated with the excited electronic state are greatly enhanced. This is helpful for studying large molecules like polypeptides, which might show hundreds of bands in "conventional" or back-scattered Raman spectra. It is also useful for associating normal modes with their observed frequency shifts [27].

3. Stimulated Raman spectroscopy

A spatially coincident, two-color pulse (with polarization either parallel or perpendicular) transfers the population from ground to a rovibrationally excited state, if the difference in energy corresponds to an allowed Raman transition, and if neither frequency corresponds to an electronic resonance [28].

4. Backscattered Raman

In Backscattered configuration information is collected back in the direction from which sample is irradiated.

5. Transmission Raman

Allows probing of a significant bulk of a turbid material, such as powders, tablets, capsules, living tissue, etc. It was largely ignored following investigations in the late 1960s but was rediscovered in 2006 as it allowed rapid assay of pharmaceutical dosage forms. There are also medical diagnostic applications [26].

6. Spatially offset Raman spectroscopy (SORS)

This spatially-offset Raman spectroscopy (SORS) is based on the multiple diffuse scattering of light in turbid media. Photons traveling through such materials can be classified in three categories: ballistic, snake, and diffuse, as represented in Figure 30(a). The photons entering the material will initially be composed of ballistic photons, which exponentially decay into snake and then diffuse photons further into the sample [26]. The first biomedical application demonstrated was the measurement of bone through several millimeters of tissue [29].

7. Tip-enhanced Raman Scattering (TERS)

TERS is inherently a hybrid optical/scanning-probe technique, relying on the ultra-precise positioning of a plasmonically-active nanoscale probe within a focused Raman excitation beam

TERS typically samples volumes of the order of 1000 nm3 thus most biological applications are targeted at separate macromolecular structures such as proteins, lipids and nucleic acids. For larger structures such as cells, only the first 10-20 nm of the surface (lipids and surface proteins) can be measured due to the evanescent decay of the near-field.

8. Hyper Raman

A non-linear effect in which the vibrational modes interact with the second harmonic of the excitation beam. This requires very high power, but allows the observation of vibrational modes that are normally "silent". It frequently relies on SERS-type enhancement to boost the sensitivity [26].

Applications

- Raman spectroscopy technique can also be used to determine the chemical composition and structure of many different samples.
- Raman microprobe spectroscopy has considerable potential as an analytical tool in orthopedic science for its capability of non-destructively assessing the physical, chemical, and mechanical characteristics of load-bearing parts in arthroplastic components (i.e., artificial joints). [30]
- Analysis of Fat components in Food without Sample Preparation.
- insensitive to aqueous absorption bands. This property of Raman facilitates the measurement of solids, liquids, and gases not only directly, but also through transparent containers such as glass, quartz, and plastic.
- Raman spectroscopy is chemically selective to different polymorphs and it is well adapted to determine which form(s) present within capsules or tablets.
- Transmission Raman spectroscopy method can also be used to test the uniformity of content in a non-destructive manner.
- Raman spectroscopy is now well-established for quantitative analysis of molecular materials of all types because it is a non-contact characterization method that does not require any sample preparation. The techniques requires little sample preparation, data is acquired quickly, it is non-destructive and water does not interfere significantly with the vibrational bands of the drugs [31].
- Raman spectroscopy has recently become one of the most popular analytical techniques used in the pharmaceutical field. It has been proved to be a valuable tool in many applications such as in polymorphic study, identification of raw materials, counterfeits detection, quantitative determination and homogeneity studies of active pharmaceutical ingredient (API) in solid dosage forms. The attention devoted to Raman spectroscopy can be explained by the possibility to quickly provide key information on the physical and chemical properties of the molecules without sample preparation. Moreover, it is a non-destructive and non-invasive technique which can be used for qualitative and quantitative analyses.[32]
- Transmission Raman Spectroscopy can probe sample depths even greater than 10 millimeters of the sample. This method is sensitive, accurate and faster and can quantitatively measure the sample.
- Transmission Raman Spectroscopy is not dependent on changes in the sample size, compaction, or presence of moisture.

Conclusion

Raman spectroscopy is a rapid, sensitive, comparatively quick and non-destructive technique and requires very little to no sample pre- preparation. Due to these advantages Raman spectroscopy can be used for identification of counterfeit medicines. It can identify the drug in counterfeit tablets regardless of its chemical composition and physical appearances. However, not all tablets and active pharmaceutical ingredients (API) show good Raman signal. This study can be utilized to gain a thorough grasp of the pharmaceutical tablet formulation, manufacturing and identification processes, which will have an effect on the entire manufacture of safe and efficient tablets for drug delivery initiatives.

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