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Review Article

Pharmaceutical Applications of Raman Spectroscopy

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ABSTRACT

In last few years Raman spectroscopy becomes essential analytical technique in various department of science. Because of technological advancement in instrumentation of Raman spectroscopy they became alternative technique for other invasive techniques for analysis. Raman spectroscopy is non-invasive, minimal sensitive to water, based on inelastic scattering of monochromatic light. Raman spectra is obtained by sample is subjecting to the laser source radiation, electron within the sample interact with radiation leads to light scattering. This review describes principle and instrumentation of Raman spectroscopy along with its pharmaceutical application. Raman spectroscopy has different applications including chemical imaging, identification and quantification of drugs, polymorphs, inorganics and minerals, In-process monitoring, medical diagnostic, analysis of drug abuse, analysis of turbid sample and also in novel drug delivery system. Advantages like minimal training to operate, simple in operating, accurate and no or minimal sample is required to analyse have made Raman spectroscopy is an charming analytical tool.

INTRODUCTION

In 1928 C.V. Raman discovered that when radiation pass through a transparent object, the object present within sample cell scatter the incident radiation in all direction. Scattered radiations wavelength is not always same as incident radiation wavelength it means incident wavelength is different than scattered wavelength. Scattering is occurs due to the changes in vibrations produced with IR absorption [1].

Changes in wavelengths depend upon the chemical structure within the sample which is responsible for light scattering. Raman awarded Nobel Prize in 1931 for this discovery. Striking of object is similar in both Raman spectroscopy and IR spectroscopy but important advantages of Raman spectroscopy is the solvent used in it. Water is useful solvent in Raman and signals are appear in the near or visible-IR region. Raman spectroscopy was not broadly used until the lasers are available for chemist in 1960s. Lasers are useful because spectra is obtained easily by using them [1].

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IR spectroscopy is the better tool for analysis but Raman spectroscopy gives superior information than the IR spectroscopy. Continuous improvement in technologies of analytical methods since last few decades, Raman spectroscopy has proven that they are useful technique in pharmaceutical field [2]. In Raman spectroscopy no sample or minimal sample preparation is required to analyse the sample. Samples in different states can be analysed such as solid, liquid and gaseous. Use of Raman in the pharmaceutical field is limited due to high price of instrumentation [3]. Some recent years Raman spectroscopy is used as routine analytical tool which uses Lasers, detectors and commercial instrumentation at reasonable cost.

Principle

Raman spectra are obtain when laser source radiation is passed through the specimen they interact with electrons present in the sample leads to light scattering. When incident light is same as scattered light then they known as Rayleigh scattering. Electrons in the ground state are goes in to the excited state by photon resulting scattering of light known as Raman scattering. After specific time excited state electrons relax down to the ground energy state.

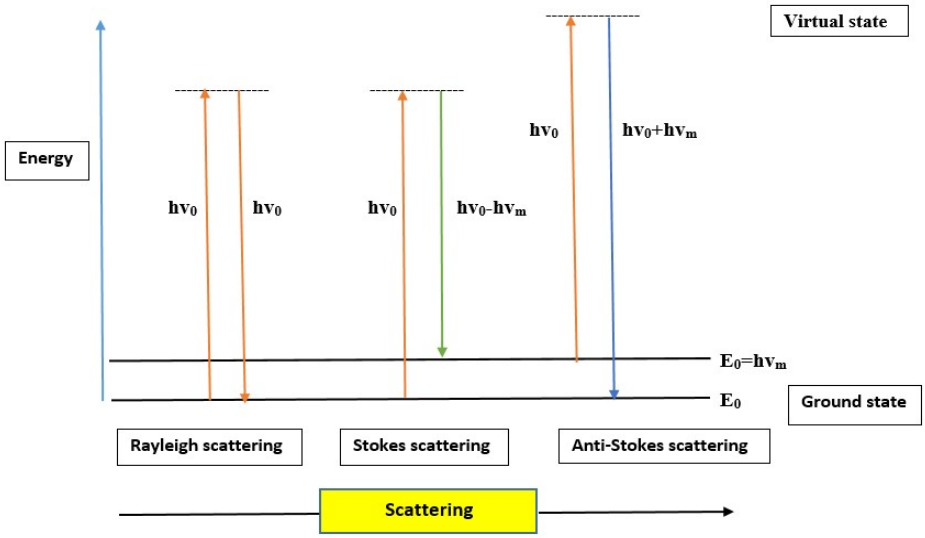

Figure 1: Origin of Raman scattering

When electromagnetic radiation is strike on the subject then thereis difference in incident light and scattered light due to the interaction between electrons present in the sample. Difference in energy among original and excited state causes shifting of wavelength.

In Stokes-Raman shift irradiated light has lower wavelength than the scattered light and in Anti-Stokes Raman shift irradiated light has higher wavelength than the scattered light [2].

Instrumentation

Instrumentation of Raman spectroscopy comprise of source, sample illumination system, Wavelength-selection Devices, Transducers (Detectors) and computer data system.

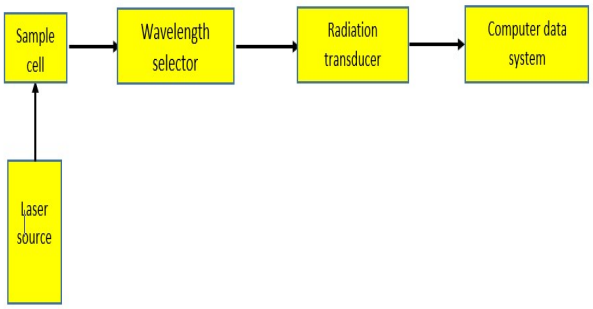

Figure 2: Block diagram of a Raman spectrometer

Sources

Lasers are used as major source in Raman spectroscopy due to their high intensity. This high intensity is essential to produce Raman scattering. Those are most useful lasers in Raman spectroscopy are listed in Table 1.

Table 1: Wavelengths of Raman Spectroscopy

Laser Type	Wavelength (nm)
Argon ion	488.0or 514.5
Krypton ion	530.9 or 647.1
Helium- neon	632.8
Diode	785 or 830
Nd-YAG	1064

Argon and Krypton ion sources has a benefit over other source, that is they are emits in blue and green region of the spectrum, as mention in table. Argon ion produce Raman lines at 488nm which is produce by He-Ne source at 632.8nm which is closely two times as intense as excited by Argon source on supply of same input power. These sources has shorter wavelength but they generate important fluorescence but has some disadvantages like they induce decomposition of the object.

Diode and Nd-YAG are emits in near-IR they are mostly used in Raman spectroscopy because of their several advantages over Argon and Krypton ion source. First advantage is that they are run at high power that is up to 50 W. Second advantage is they do not decompose the sample at high power [1].

Sample Illumination System

In Raman spectroscopy glasses can be used alternate to the crystalline halides for window, lenses which are less stable than glass hence the

handling of sample in Raman is simpler than IR spectroscopy.

- **Gas samples:** Glass tubes about 1-2 cm in diameter and 1mm thick are used for gaseous samples. Small capillary tubes are also used for gases.
- **Liquid samples:** Ampoules, capillaries or glass tubes are used to seal liquids. Capillaries are about 0.5-0.10 mm hole and about 1 mm long. Small sample of liquid that is about nanoliter volumes can produces spectra by using capillary cells.
- **Solid sample:** Solid sample is filled in capillary or small cavity which is converted in to thin powder and spectra is obtained. KBrpellets are also used in Raman spectroscopy which is same as used in IR spectroscopy which reduce decomposition of the sample.

Raman Microprobe

In Raman spectroscopy microprobe is an important part, now a days different companies make its attachments which is used to keep the sample over the stage microscope. In 1970s the first microscopy of the Raman was developed. Sample is ablaze by visible light. Firstly select the area which is analyse and adjust the focus, ablaze lamp is turned off and lasers are strike on the sample [1].

Wavelength-selection Devices and Transducers

Powerful grade monochromator are obligatory to separate the weak Raman lines and Rayleigh-scattered radiation. Traditional Raman instrumentation include double or triple grating monochromators for selecting specific wavelength and also differentiate weak lines with scattered radiation.

Notch filters is also known as holographic interference filter. Newer holographic gratings avoid the use of multiple grating monochromator. Photomultiplier and Photodiode array is used as transducers (detectors) in Raman spectroscopy. Monochromators along with photomultiplier tubes which is used as detectors is superior because they are capable to measure weak signals. Single wavelength monochromator is substituted by spectrograph and photodiode array detectors in newly Raman instrument which is able to the instantaneous accumulation of the complete Raman spectra [1]. Spectra obtained in Raman spectroscopy are gathered in visible region by dispersive Raman detector or in Near IR region by Fourier Transform Raman detector. Obtained spectra are divided into components wavelength for analysis. Spectra is defined as intensity vs frequency plot [2].

Advantages

Raman spectroscopy is a precious process analytical tool in pharmaceutical sector.

- It's minimal sensitive to water, accurate and non-invasive technique.
- It requires minimal training to operate and it is comparably simple to operating.
- They require nominal sample and not interfered by water.
- One of the major advantage of Raman spectroscopy is that they analyse sample present within their packaging material [1].

Limitations

- Thermal decomposition of sample is occur when high intensity of source is used.
- Overlays of bands occur during measurement of spectrum because of high level of fluorescence occur in visible region caused by impurities which is overcome in NIR region [4].
- Due to light penetration on the sample only small fraction of sample (tablet) interact with light hence the signals produced are not of full sample (tablet contents) [5].

Surface Enhanced Raman Spectroscopy (SERS)

Surface enhanced Raman spectroscopy is the advancement in the Raman spectroscopy which is capable to detecting the low dose substances present in the pharmaceutical sample. It is more sensitive and have a greater advantages over Raman spectroscopy. They able to increase the scattering from sample [6]. Detection and quantitative analysis id done by using SERS. It solves the problem related fluorescence in Raman spectroscopy [5].

Pharmaceutical Application

Quality control with SERS: SERS is more preferred analytical tool because it is more sensitive and specific technique for quality control. It is used to detect and identify impurities in the sample and also drugs in low dose. SERS is used to detect homogeneous mixture of active ingredient and additives in the formulation [6]. Raman spectroscopy has ability

to analyse the sample within their packaging material which helps in time and cost saving. SERS detected antibiotics which are present in the food [7].

Chemical imaging by SERS: Using SERS chemical imaging we determine the location of low dose compounds and also visualize their distribution in formulation [6].

Identification and quantification of drugs: Due to high sensitivity of SERS some illicit and stimulant drugs (synthetic) can be identified with very low detection limit, E.g., Amphetamine, methamphetamine and their derivatives. Identification and monitoring of drug concentration in biofluids, also detect traces of allergen which is responsible for allergic reaction [6].Quantitative analysis of solid-state formulation is done by Raman spectroscopy in which one of the reported work of quantitative analysis on the simultaneous analysis of paracetamol and phenylpropanolamine hydrochloride is available [8].

Quantifying polymorphs in pharmaceutical formulations: During manufacturing of formulation of crystalline components, polymorphism may occur. Raman spectroscopy is important technique to quantify polymorphs which provide solid state information of formulation. It is also useful to analyse the drug residue in the environment [5]. Identification and Quantification of anthelmintic drugs i.e. mebenda-zolefrom the raw material used by the industry [9].

Inorganics and Minerals: Raman is valuable technique to examine the inorganic materials, which is capable to identify and characterise both elements and molecule [10].

Testing the mechanical strength of tablets: To determine the hardness of tablet there are several methods available, but they are invasive. Raman spectroscopy is a non-invasive technique used to find different properties of tablet [11].

In situ monitoring of co-crystals in formulation development: Low-frequency (LF) Raman spectroscopy is used to monitor co-crystals or polymorphs. NIR and conventional Raman spectroscopy do not provide information of crystal lattice directly because they have high sensitivity towards local environment changes [12].

Industrial Applications

Raman spectroscopy is useful tool in R&D which gives needful information about nature of material. In quality Assurance it is used to monitor gases present in the headspace of the sealed vials [13].

In-process monitoring using Raman and NIR spectroscopy: Raman spectroscopy is useful tool for the in-line and real time in-process monitoring. End point detection in powder blending process is monitored by Raman spectroscopy [14].

a. API and excipients of formulation are subjected to different process such as blending, granulation, drying, milling, coating and packaging before formulation development. Raman spectroscopy is also used to monitor pelletization process [15].

b. Laser-induced breakdown spectroscopy (LIBS) is used to monitor In-process but it may cause to tablet because laser radiation and shock wave convert tablet into its fragments. Raman spectroscopy is superior than LIBS due to it is non-invasive technique and spectra are acquired in less than one second [16].

Analysis of the API distribution and excipients in final medicinal products: Stability and functionality of formulation depends on the distribution of API and excipients. Raman spectroscopy enables visualization of chemical, spectral information of excipients in the intact dosage form [17]. API detection in micro tablets is carried out by Raman spectral imaging techniques [18].

Characterization of aqueous colloidal systems by Raman spectroscopy: Lipid is important constituents in many colloidal systems. Characterization of colloids is done by using Raman spectra of lipids which is sensitive to dynamical changes involving in hydrocarbon chains [19].

Medical diagnostics: Raman spectroscopy is alternative technique to the novel analytical approaches to detect and identify pathogens in the blood or urine [20].

In novel drug delivery systems: FT-Raman is used to characterize nanostructured lipid carriers (NLCs) and solid lipid nanoparticles [21]. For characterization of nanosensor, nanotube

and nanowire Raman spectroscopy is relevant tool in nanotechnology [22].

Analysis of drugs of abuse: Barbiturates and sodium salt analogs can be analysed by using Raman spectroscopy, E.g., Phenobarbital, barbital, amobarbital, secobarbital. Raman spectrophotometer equipped with fibre optic Raman probe is used to identification of free base cocaine and cocaine hydrochloride [23].

Coating characterization by Raman spectroscopy: Fluorescent coating of tablet is studied by Raman spectroscopy. Coating quantification under fluorescent condition is analysed by Raman spectroscopy along with appropriate data [24].

Raman spectroscopy in pharmaceutical product design: For early drug development preformulation study of candidate drug is essential, which gives data related to physico-chemical properties of drug candidate. Raman spectroscopy is used to understand phase changes such as polymorphic changes, amorphization [25].

Non-invasive Analysis of Turbid Samples: Spatially Offset Raman Spectroscopy (SORS) is used to analyse the turbid samples. It collects Raman signals away from laser illumination area. They collect signals on sample surface separated by 'spatially Offset' upon penetration depth [26].

CONCLUSION

Raman spectroscopy is used an effective analytical tool which was discovered by C. V. Raman in 1928. Raman has several advantages like accuracy, non-invasive, ease interpretation of data and sensitive they make this technique more useful in pharmaceutical field. From above data we conclude that Raman is an emerging technique in the process analysis. They have number of application in pharmaceutical areas such as chemical imaging by SERS, identification and quantification of drugs, polymorphs, inorganics and minerals, In-process monitoring, medical diagnostic, analysis of drug abuse and analysis of turbid sample.

REFERENCES

[1] Skoog, D.A., Holler, F.J. and Crouch, S.R., 2007. Instrumental analysis (pp. 533-550). Belmont: Brooks/Cole, Cengage Learning.

[2] Title: Emerging technologies for the non-invasive characterization of physical-mechanical properties of tablets Authors: Vivek S. Dave, Hend I. Shahin, Susanne R. Youngren-Ortiz, Mahavir B. Chougule, Rahul V. Haware

[3] Rantanen, J., 2007. Process analytical applications of Raman spectroscopy. Journal of Pharmacy and Pharmacology, 59(2), pp.171-177.

[4] Paiva, E.M., da Silva, V.H., Poppi, R.J., Pereira, C.F. and Rohwedder, J.J., 2018. Comparison of macro and micro Raman measurement for reliable quantitative analysis of pharmaceutical polymorphs. Journal of pharmaceutical and biomedical analysis, 157, pp.107-115.

[5] Alula, M.T., Mengesha, Z.T. and Mwenesongole, E., 2018. Advances in Raman spectroscopy for analysis of pharmaceuticals: A review. Vibrational Spectroscopy.

[6] Cailletaud, J., De Bleye, C., Dumont, E., Sacré, P.Y., Netchacovitch, L., Gut, Y., Boiret, M., Ginot, Y.M., Hubert, P. and Ziemons, E., 2017. Critical review of surface-enhanced Raman spectroscopy applications in the pharmaceutical field. Journal of pharmaceutical and biomedical analysis.

[7] Li, Y.S. and Church, J.S., 2014. Raman spectroscopy in the analysis of food and pharmaceutical nanomaterials. Journal of food and drug analysis, 22(1), pp.29-48.

[8] Strachan, C.J., Rades, T., Gordon, K.C. and Rantanen, J., 2007. Raman spectroscopy for quantitative analysis of pharmaceutical solids. Journal of pharmacy and pharmacology, 59(2), pp.179-192.

[9] Virtanen, S., Antikainen, O. and Yliruusi, J., 2008. Determination of the crushing strength of intact tablets using Raman spectroscopy. International journal of pharmaceutics, 360(1-2), pp.40-46.

[10] Vankeirsbilck, T., Vercauteren, A., Baeyens, W., Van der Weken, G., Verpoort, F., Vergote, G. and Remon, J.P., 2002. Applications of Raman spectroscopy in pharmaceutical analysis. TrAC trends in analytical chemistry, 21(12), pp.869-877.

[11] Otaki, T., Tanabe, Y., Kojima, T., Miura, M., Ikeda, Y., Koide, T. and Fukami, T., 2018. In situ monitoring of cocrystals in formulation development using low-frequency Raman spectroscopy. International journal of pharmaceutics, 542(1-2), pp.56-65.

[12] Gilbert, A.S. and Lancaster, R.W., 2017. IR and Raman Spectroscopy, Industrial Applications.

[13] Dent, G. and Smith, G., 2005. Modern Raman spectroscopy: a practical approach. Wiley.
[14] Riolo, D., Piazza, A., Cottini, C., Serafini, M., Lutero, E., Cuoghi, E., Gasparini, L., Botturi, D., Marino, I.G., Aliatis, I. and Bersani, D., 2018. Raman spectroscopy as a PAT for pharmaceutical blending: Advantages and disadvantages. Journal of pharmaceutical and biomedical analysis, 149, pp.329-334.
[15] De Beer, T., Burggraeve, A., Fonteyne, M., Saerens, L., Remon, J.P. and Vervaet, C., 2011. Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. International journal of pharmaceutics, 417(1-2), pp.32-47.
[16] Williams, J.A.S. and Bonawi-Tan, W., 2004. Online quality control with Raman spectroscopy in pharmaceutical tablet manufacturing. Journal of manufacturing systems, 23(4), pp.299-308.
[17] Mazivila, S.J. and Olivieri, A.C., 2018. Chemometrics coupled to vibrational spectroscopy and spectroscopic imaging for the analysis of solid-phase pharmaceutical products: A brief review on non-destructive analytical methods. TrAC Trends in Analytical Chemistry.
[18] Kandpal, L.M., Cho, B.K., Tewari, J. and Gopinathan, N., 2018. Raman spectral imaging technique for API detection in pharmaceutical microtablets. Sensors and Actuators B: Chemical, 260, pp.213-222.
[19] Wartewig, S. and Neubert, R.H., 2005. Pharmaceutical applications of Mid-IR and Raman spectroscopy. Advanced drug delivery reviews, 57(8), pp.1144-1170.
[20] Popp, J. and Windbergs, M., 2015. Preface: Pharmaceutical applications of Raman spectroscopy—From diagnosis to therapeutics. Advanced drug delivery reviews, (89), pp.1-2.
[21] Gala, U. and Chauhan, H., 2015. Principles and applications of Raman spectroscopy in pharmaceutical drug discovery and development. Expert opinion on drug discovery, 10(2), pp.187-206.
[22] Das, R.S. and Agrawal, Y.K., 2011. Raman spectroscopy: recent advancements, techniques and applications. Vibrational spectroscopy, 57(2), pp.163-176.
[23] Bumbrah, G.S. and Sharma, R.M., 2016. Raman spectroscopy–Basic principle, instrumentation and selected applications for the characterization of drugs of abuse. Egyptian Journal of Forensic Sciences, 6(3), pp.209-215.
[24] Romero-Torres, S., Pérez-Ramos, J.D., Morris, K.R. and Grant, E.R., 2006. Raman spectroscopy for tablet coating thickness quantification and coating characterization in the presence of strong fluorescent interference. Journal of pharmaceutical and biomedical analysis, 41(3), pp.811-819.
[25] Paudel, A., Raijada, D. and Rantanen, J., 2015. Raman spectroscopy in pharmaceutical product design. Advanced drug delivery reviews, 89, pp.3-20.
[26] Matousek, P., 2018. Spatially offset Raman spectroscopy for non-invasive analysis of turbid samples. TrAC Trends in Analytical Chemistry.