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Raman spectroscopy in pharmaceutical product design ☆

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ABSTRACT

Almost 100 years after the discovery of the Raman scattering phenomenon, related analytical techniques have emerged as important tools in biomedical sciences. Raman spectroscopy and microscopy are frontier, non-invasive analytical techniques amenable for diverse biomedical areas, ranging from molecular-based drug discovery, design of innovative drug delivery systems and quality control of finished products. This review presents concise accounts of various conventional and emerging Raman instrumentations including associated hyphenated tools of pharmaceutical interest. Moreover, relevant application cases of Raman spectroscopy in early and late phase pharmaceutical development, process analysis and micro-structural analysis of drug delivery systems are introduced. Finally, potential areas of future advancement and application of Raman spectroscopic techniques are discussed.

Contents

1. Introduction

Since 1928, when Raman and Krishnan discovered the new type of secondary radiation later termed "Raman scattering", there has been a constant flow of development in the instrumentation using this principle. With the advancements in photonics and optoelectronics, as well as a rapidly expanding range of applications, Raman spectrometers, microscopes and allied analytical tools have continuously evolved over the decades [1]. Several efforts in spectrometric hardware have invested in tackling the intervention of the stronger elastic Rayleigh

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signal to the weaker Raman (inelastic) scattering signal. These efforts have resulted in the highly efficient Rayleigh line filters [2]. Historically, the developments of Raman tools were also augmented by the discoveries of various phenomena other than the basic Raman effect, such as resonance Raman (RR), coherent anti-Stokes Raman scattering (CARS) and surface-enhanced Raman scattering (SERS) [1]. Raman spectroscopy has proven to be a useful tool in a vast number of fields, including pharmaceuticals, in vivo biomedical studies, process control, environmental sciences, semiconductors, catalysts, glasses, pigments, archaeology and forensic sciences. Raman analytical techniques have been increasingly implemented at different stages of drug discovery and development. This includes chemical identification, molecular biology research and diagnostics, preformulation, solid form screening, bioanalysis, formulation analytics in late phase drug development, process analytics, quality control, raw material qualification and counterfeit identification.

The analytical versatility of Raman molecular spectroscopic techniques allows for investigating a wide diversity of transparent, translucent, opaque, and coloured samples including solids, semi-solids, suspensions, and solutions. This facilitates non-invasive analysis of synthetic reaction mixtures, biological specimens, and intermediates to various finished dosage forms (such as powders, tablet/capsule, creams, heterogeneous suspensions, and syrups) with minimal or no sample preparations [3]. Spontaneous instrumental evolutions of Raman-based techniques have progressed from traditional laboratory spectrometers to a wide range of miniaturized and tunable lasers, optical filters, spectrographs, interferometers, charge-coupled device (CCD), microprocessor control and Raman probes. These have improved the mobile applications to be non-contact, process-friendly and allow for remote analysis through glass containers, well plates, and even aqueous samples [4]. Today, Raman-based tools are cheaper, smaller, smarter and faster, and the analysis of "real world samples" in-line from production lines or inside the packaged containers has gone from a concept idea to a well-established practice for different pharmaceutical products [5]. This has led to the recognition of Raman spectroscopy by regulatory authorities for innovative analysis.

Spectral analysis of pharmaceuticals using Raman-based techniques presents some additional benefits over mid- or near-infrared (IR) spectroscopy. Because Raman spectroscopy is a scattering technique, there is no need for a reference light path (as needed for IR/NIR); therefore, it is amenable to fibre optics and allows for remote sampling. Higher lateral spatial and depth resolution is attainable by (confocal) Raman microscopy than by IR microscopy. In many ways, it is possible to characterize samples better than with Fourier-transform IR (FT-IR) spectroscopy. However, any possible fluorescence from the sample should be taken into consideration. A single scan of a typical Raman measurement can collect spectral data in the range of 4000–40 cm^{-1}. In addition to the fingerprint region between 4000 and 400 cm^{-1}, the low frequency or far IR region (400–40 cm^{-1}) of Raman spectra covers some of the important vibration modes that are relevant for the identification of different solid-state forms [6]. Water being a weak Raman scatterer makes it possible to successfully analyze aqueous samples by Raman spectroscopy. In many cases, sharper spectroscopic contrast between API and excipients offer superior quantitative analysis capability.

Raman spectrometers comprise a laser light source, focusing optics, and spectrograph(s) consisting of a dispersing element and a detector [2,7]. The diverse Raman laser sources deliver in the range of UV to NIR region, the most ubiquitous being the visible light laser [8]. As Raman efficiency is inversely related to the fourth power of the wavelength, the selection of a suitable source requires the accounts of sample nature and the spectrometer geometry. Additionally, samples with possible fluorescence interference require a longer excitation wavelength. Dispersive Raman spectrometers utilize a holographic grating monochromator as the spectrograph, whereas FT-Raman instruments typically utilize the Michelson interferometers. A Raman detector is generally a photon collecting photomultiplier tube/CCD or a germanium detector (FT-Raman). Raman microscopes are equipped with a conventional optical microscope as a sampling device and thus can perform localized sample analysis, enabling hyperspectral chemical imaging by wide field imaging or line/point mapping [1]. Furthermore, confocal Raman microscopy (CRM) can axially discriminate signals originating from selective depth within the sample using the confocal hole [9]. The fundamental working principles and components of Raman instrumentations, from conventional to advanced instrumentations, are available in many standard books and excellent review papers [1,4,7,8,10]. We have excluded the basic quantum process associated with various types of Raman scattering phenomena, but these are also covered in many books and papers. Because the present review aims to provide a broad perspective on the application of various Raman tools in drug development, only very brief accounts are reported [11].

2. Enabling development of Raman techniques

2.1. Raman sampling configurations

Different existing Raman sampling geometries are schematically illustrated in Fig. 1. A traditional backscattering Raman analysis acquires data from a small spot of an analyte. Therefore, the resulting spectral output may fail to entirely represent the static and heterogeneous sample. Sample rotation during spectral acquisition and the temporal averaging of the acquired data, the spatial averaging of the data acquired by scanning different regions of sample, and simultaneous wide-angle illumination (WAI) are configurations available to overcome the issues related to sub-sampling [12–14]. Most analysis of pharmaceutical solid samples utilizes WAI, which involves the illumination of a large volume of samples using wider laser beam and selective collection of Raman scattering within the covered area. A dispersive Raman probe constituting multiple optical fibres, known as PhAT (Pharmaceutical Area Testing), measures a significantly larger sample volume [12,15]. Furthermore, the configuration enabling the collection of signals from locations laterally offset away (hundred micrometres to centimetres in some cases) from the illuminated area is called spatially offset Raman spectroscopy (SORS) [16]. Typical SORS geometry irradiates the laser at the centre of the ring and Raman collection from the circumference, the radius being the spatial offset [17]. The avoidance of surface interference with this technique can facilitate the depth profiling of the sample. Spectral acquisition representing a bulk sample can be performed using transmission Raman spectroscopy (TRS), wherein the incident and the collection beam path are separated to the extreme on opposite sides of sample [18]. TRS potentially avoids the sub-sampling problem of heterogeneous samples and yields (semi) averaged spectral data of the bulk composition for turbid or opaque materials [19–23].

Surface-enhanced Raman scattering (SERS) and tip-enhanced Raman scattering (TERS) are extensively researched and implemented surface-sensitive Raman techniques [24–27]. In brief, a SERS signal enhances via dipolar localized surface plasmon resonance originating from the interaction of visible light and a nanoscale rough surface noble-metal substrate coated with analyte [28]. The interaction of sample with the intense electric field generated from substrate-incident light interaction increases the magnitude of induced dipole of the sample, thus enhancing the Raman scattering signal [24]. TERS is a high resolution SERS variant combined with atomic force microscopy (AFM) for the localization of incident light at sufficient proximity to the analyte [29–31]. The surface plasmon excited at a sharp-metal tip brought onto the sample surface initiates the SERS effect upon laser irradiation [32]. In addition to surface sensitive Raman techniques, signal enhancing Raman nonlinear techniques such as coherent anti-Stoke Raman scattering (CARS) are increasingly used for the spectroscopic imaging of pharmaceuticals [33,34]. CARS technique involves a coherent

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