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Recent developments in the Raman and infrared investigations of amorphous pharmaceuticals and protein formulations: A review☆

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ABSTRACT

The success rate for drug discovery and the development of innovative therapeutic strategies are intimately related to the physical properties of the solid-state condensed matter, which have direct influence on the bioavailability of Active Pharmaceutical Ingredients. In order to transform a new molecule in efficient drug, the material is brought into an amorphous state using various manufacturing processes including freeze drying, spray drying, hot melt extrusion and loading in different delivery devices. The infrared and Raman spectroscopic analyses used for exploring disordered and amorphous states, for the monitoring of the drug physical stability in drug delivery systems are described in this review.

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1. Introduction

It is well recognized that the physical state of an active pharmaceutical ingredient (API) is closely related to their bioavailability, and knowledge about its stability conditions are crucial to respect the drug dosage. Numerous new drug candidates are characterized by a poor solubility in crystalline states and require amorphization in special dosage forms for enhanced bioavailability [1]. However, the amorphous state is metastable with respect to the crystalline state, and may spontaneously recrystallizes under stress induced by manufacturing processes, or by storage conditions [2–4] (humidity, temperature). The determination

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of the stability conditions of amorphous formulations, requires to understand excipient — API interactions, and also the monitoring through the several stages of processing as solid-dosage forms.

Raman and near infrared (NIR) spectroscopies are recognized as non-destructive tools for both process analytical technology (PAT) [5, 6] applications and in quality control laboratories for stability analysis. Both spectroscopic techniques enable the enhancement of process knowledge for solid, liquid and biopharmaceutical forms [7, 8]. Combined with chemometric tools, they are very sensitive and complementary indirect structural probes, which provide information on molecular conformation and molecular packing in disordered and complex systems.

Interaction between light and matter can result in absorption, scattering or no interaction of the incident photon with the material which may pass through it without any change. Absorption and scattering processes are presented in Fig. 1. Absorption requires that the energy of the incident photon corresponds to the energy gap between the ground state and a higher energy level of the molecule. The process of absorption spectroscopy is used in various techniques including infrared spectroscopy. In this technique, infrared energy covering a range of frequencies is used as radiation. By contrast, the scattering phenomenon does not require that the photon energy matches the difference between two energy levels of the molecule. Two types (elastic and inelastic) of scattering can occur, in which the energy photon is transferred to the molecule, promoted in a short-lived (called virtual) vibrational energy level. In the case of elastic scattering, the photon energy is spontaneously re-emitted without energy change; this phenomenon is called Rayleigh scattering. In the inelastic scattering process the energy photon is re-emitted with an energy lower or a higher than the incident radiation energy, corresponding to the anti-stokes or stokes Raman scattering. Raman scattering requires a monochromatic radiation from a laser source. Infrared absorption and Raman scattering are two vibrational spectroscopies providing similar information on molecular vibrations. However, the use of two different types of radiation has important consequence on the selection rules of the vibrational modes. Infrared absorption requires that a vibrational mode of the molecule induces a change in the dipole moment, i.e. in the charge distribution within the molecule, to be IR active. In contrast the electromagnetic radiation associated with the laser source momentary distorts the electronic cloud distributed around a bond within a molecule. As a result, the vibrational mode of the bond will be Raman active if the vibration induces a distortion of the electronic distribution around the bond, and causes large polarization change, i.e. a polarizability change. The Raman activity of vibrational modes is dependent on parameters influencing polarizability, and marking pronounced differences with IR spectroscopy. Symmetric vibrations induce the largest polarizability change and give the greatest Raman scattering, while asymmetric vibrations cause more significant change in the charge distribution and then IR absorption activity. This difference is responsible for advantages or disadvantages of one of two techniques, with interesting use in the domain of pharmaceutical applications. Water vibrations give an intense contribution to the IR spectra, which forces to eliminate the presence of moisture even in low proportion. Additionally, the analysis of aqueous solution by IR spectroscopy is highly perturbed by the stretching and bending bands of water. On the other hand, Raman scattering can generate specific excitations when the virtual states are overlapping with excited states (Fig. 1). This can induce interesting enhanced Raman intensity of specific vibrational bands (resonant Raman scattering) or intense interference signal (fluorescence) depending on the timescale of the virtual state (~10^{-14} s for scattering and ~10^{-8} s for fluorescence). Polarizability is proportional to the number of electrons, to the molecular size, and inversely proportional to the bond strength. Generally, Raman scattering intensity is much larger for π systems than σ bonded structures, making Raman spectroscopy very sensitive for analyzing APIs compared with excipients.

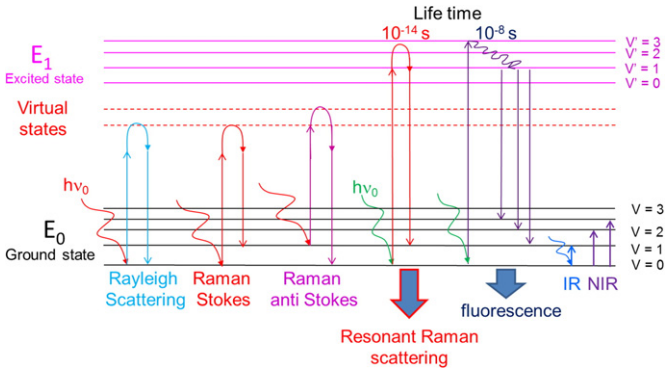

Fig. 1. Description of Raman effect, fluorescence, resonant Raman effect, IR and NIR absorption.

For many years the IR spectroscopy has been widely used with respect to the Raman spectroscopy, largely due to the cost of the lasers. Nowadays, the advances in notch-filter and diode laser technologies have resulted in new Raman spectrometers accessible to non-expert users, and this technique becomes industry standard with advantages with respect to IR spectroscopy. The most significant advantage of Raman spectroscopy is that no specific sample preparation is required without care of moisture, making possible the analysis of tablets or powders as obtained from manufacturing process, or almost in-situ from in line manufacturing process. Raman spectroscopy gives the opportunity to investigate low-frequency domains down to ~2 cm^{-1}, while far-IR spectroscopy is limited to the 100–400 cm^{-1} range. It is an undeniable advantage of Raman spectroscopy which makes it possible the analysis of low-frequency excitations distinctive of the amorphous state. Selecting the use of one of the two spectroscopic techniques was discussed by De Beer et al. [5].

In this review, the capabilities of Raman and NIR spectroscopy to carefully describe the physical state of different kinds of disordered systems, especially amorphous states and mixed amorphous — (macro, micro, nano) crystalline states, will be shown. The contribution of IR and Raman spectroscopy to the analysis of protein formulations in solutions and in the solid state will be presented. The description of the THz spectroscopy methods was deliberately omitted since it's the subject of another review.

2. Description of the different kinds of motions in molecular systems

Considering a molecule as a rigid body, three different kinds of motions can exist in disordered organic solids, and only the access of the low-frequency region (below 100 cm^{-1}) gives the opportunity to analyze these different kinds of motions.

The internal motions correspond to vibrations of interatomic bonds within the molecule. They are mainly distinctive of the molecular conformation in the fingerprint region, usually lying between 500 and 1800 cm^{-1}, and corresponding to the region where the vibrations of the molecular skeleton are active. Generally, a molecule composed of N atoms has 3 N-6 vibrations, 3 N-5 for linear molecules. If the molecule is placed in crystalline lattice, the 3 N-6 vibrations generates a number of Raman and IR vibrational bands higher than 3 N-6, depending both on the crystalline and the molecular symmetries, i.e. the so-called site symmetry. The increase of the degree of disorder in a crystal induces higher lattice symmetry, and thus less and broader vibrational bands. Consequently, the spectrum of internal vibrations can be used as a sensitive probe of the local molecular environment, i.e. to the degree of disorder, by counting the vibrational modes, or/and by analyzing the bandshape of Raman or IR active modes. The spectrum of an amorphous state corresponds to the spectrum of the isolated molecule, and then is usually composed of 3 N-6 bands. Internal Raman or IR spectrum makes it possible the evidence of molecular associations via hydrogen bonds (H-bonds). Polymorphism in molecular compounds including