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Vibrational spectroscopy used in polymorphic analysis

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ABSTRACT

Vibrational spectroscopy includes several techniques, the most important being mid-infrared (MIR), near-IR (NIR) and Raman spectroscopies. Vibrational spectrometry covers a series of well-established analytical methodologies suitable for both qualitative and quantitative purposes. Raman and MIR spectroscopies are complementary techniques and usually both are required to measure the vibrational modes of a molecule completely. In the first part of this review, we focus on theoretical aspects related to vibrational techniques, while, in the second part, we discuss important articles published during the period 2000–14 relating to polymorphic analysis.

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1. Introduction

"Polymorphism" comes from the Greek word, *polus* = many and *morph* = shape, so it is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice. It essentially means that, in different polymorphs, the same molecule exists in different ways (i.e., a material that exhibits different crystal structures within the solid state but has identical characteristics in solution). Polymorphism is a technical term used in biology and crystallography. It is estimated that 80–90% of organic compounds are capable of existing in polymorphic forms.

As a result of the polymorphism phenomena, the molecules can present different arrangements in the unit crystal cell and can thus have different physical properties [1], including packing, thermodynamic (e.g., solubility, free energy, and melting point), spectroscopic, kinetic properties (e.g., dissolution rate and stability), and mechanical (e.g., hardness, compatibility, tableting, and tensile strength). Polymorphism is very important in those areas of chemical research where full characterization of a material has a pivotal role in determining its ultimate use (e.g., pharmaceutical, pigment, agrochemical, explosive and fine-chemical industries) [2].

Taking into account the pharmaceutical literature, it is very clear that the physical characterization of the active principle ingredient (API) is crucial for the development of each drug [3,4]. It has been known for a long time that a pharmaceutical can exist in more than one solid form (i.e., crystal or amorphous). The different solid forms of a drug can display significantly different physical and chemical properties, including color, morphology, stability, dissolution, and bioavailability [5]. These properties can have direct effects on the ability to process and/or manufacture the drug substance and the drug product, and drug-product stability, dissolution and bioavailability. Polymorphism can affect quality, safety and efficacy of the drug product [2,6]. The most thermodynamic stable form is chosen for development of the final dosage product, but, more recently, metastable forms were used to enhance dissolution or bioavailability profiles. For example, carbamazepine is a poorly soluble drug that exists in four well-characterized anhydrous crystal

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forms [i.e., P-monoclinic (III), triclinic (I), trigonal (II) and C-monoclinic (IV)]. The P-monoclinic polymorph is marketed in commercial preparations because it is relatively stable at ambient temperature and has higher solubility and bioavailability, while the C-monoclinic polymorph can be formed under various conditions possible during drug formulation.

Piracetam is a nootropic drug that has five reported polymorphs, and at least two hydrated forms (a monohydrate and a dihydrate). Two forms, FIV and FV are generated under high pressure while FI is generated when FII or FIII is heated to 127°C (below the melting points of both polymorphs) and then quenched to room temperature. The FII and FIII polymorphs are both kinetically stable at room temperature and FIII is the thermodynamically more stable polymorph with FII being metastable.

In the past, physical characterization of the API was especially performed with optical microscopy, X-ray powder diffraction (XRPD) and thermal analysis, including differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). After 1940, infrared (IR) spectroscopy became one of the most used techniques in the multi-disciplinary approach to physical characterization of pharmaceutical solids, while recently Raman and solid-state nuclear magnetic resonance (ssNMR) spectroscopy also became used for solid-state characterization. In addition, time-of-flight secondary ion mass spectrometry (TOF-SIMS) was added to these techniques to achieve better characterization of solids [7].

Chemical imaging can also be achieved using IR and Raman spectroscopy with the additional advantage that a specific component can be located within a drug product based upon spectral response, and the spectra can also potentially differentiate different solid forms of the API [8].

The polymorphic behavior of drugs is a major concern of the pharmaceutical industry as it may have considerable formulation, therapeutic, legal and commercial implications [9], so it is crucial to be able to identify and to quantify different polymorphic forms of drugs adequately.

Since polymorphic forms are generally extremely sensitive to physical treatments, such as milling, grinding or heating, many physico-chemical techniques are not useful in the study of substances that can undergo polymorphic transitions. The main advantage of Raman spectroscopy is that no sample manipulation is required, so, in the case of polymorphs that are susceptible to transformation, the spectra can be obtained with complete certainty of the identity of the sample under investigation. The absence of sample preparation makes Raman spectroscopy a more robust testing procedure [10].

The appropriate vibrational spectroscopy measuring mode (IR or NIR) will be dictated by the optical properties of the samples (Fig. 1). Transparent materials are usually measured in transmittance mode (Fig. 1A). Turbid liquids or semi-solids and solids may be measured in diffuse transmittance mode (Fig. 1B), diffuse reflectance mode (Fig. 1C) or transflectance mode (Fig. 1D and E), depending on their absorption and scattering characteristics.

Every molecule has a unique fingerprint of vibrational frequencies, which makes Raman and Fourier-transform IR (FTIR) spectroscopy highly specific techniques for molecular identification. Both techniques can be employed non-invasively, making them ideal for any applications. Raman and FTIR spectroscopy are sometimes referred to as “sister” techniques and provide complementary information about molecules, but they differ in fundamental ways.

Polymorphism is a widespread phenomenon in polymers; under the right conditions, almost all semi-crystalline polymers can form polymorphs. Biodegradable polymers have attracted increasing interest in fundamental research and technology, due to their potential to address environmental concerns and biomedical applications. Biodegradable polymers break down in physiological environments by macromolecular chain scission into smaller fragments, and ultimately into simple, stable end-products. The degradation may be due to aerobic or anaerobic microorganisms, biologically active processes (e.g., enzyme reactions) or passive hydrolytic cleavage [11].

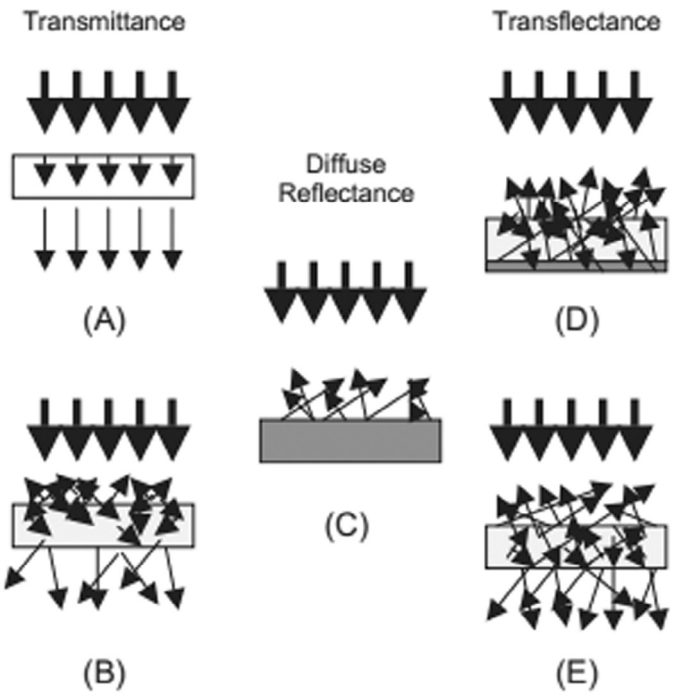

Fig. 1. Infrared spectroscopy measuring modes: (A/B) transmittance, (C) diffuse reflectance and (D/E) transflectance.

The objective of this article is to review new developments in applications of vibrational spectroscopy (Raman and FTIR) in polymorphic analysis, covering the period 2000–14. Prior to the review, it is useful to give a short introduction to the concept of the vibrational spectroscopy followed by discussion of the quantitative and qualitative applications of these techniques.

2. Theoretical aspects

Vibrational spectroscopy includes several different techniques, but the most important techniques are mid-IR (MIR), near-IR (NIR), and Raman spectroscopy. Both MIR and Raman spectroscopies provide characteristic fundamental vibrations that are employed for the elucidation of molecular structure and are the topic of this review. NIR spectroscopy measures the broad overtone and combination bands of some of the fundamental vibrations (only the higher frequency modes) and is an excellent technique for rapid, accurate quantitative determination.

Vibrational spectroscopy offers complete information on the chemical composition of samples regarding both major and minor compounds, which present many characteristic bands in the range studied. Additionally, the presence of trace compounds can be modeled in some cases through the multivariate treatment of the whole IR or Raman spectra of well-characterized samples based on the influence of molecules at low-concentration levels on the size and the shape of the bands of major compounds.

Molecular vibrations can be excited via two physical mechanisms (i.e., the absorption of light quanta and the inelastic scattering of photons), as can be seen in Fig. 2.

Direct absorption of photons is achieved by irradiation of molecules with polychromatic light that includes photons of energy matching the energy difference between two vibrational energy levels [i.e., the initial (ground state) and the final (first excited state)