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Optical properties of Meloxicam in the far-infrared spectral region

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ABSTRACT

One of the most commonly used nonsteroidal anti-inflammatory active pharmaceutical ingredient called Meloxicam has been characterized spectroscopically both by Terahertz (THz) time domain spectroscopy (THz-TDS) and by Fourier Transform Infrared (FTIR) spectroscopy in far-IR regions of electromagnetic spectrum; 0.2 THz–20 THz. While many relatively sharp features are observed in the far-IR range between 2 THz–20 THz as expected for being an organic substance, very distinct and relatively strong absorption bands are also observed at 1.00, 1.66, 2.07 and 2.57 THz in the THz range. These well separated, defined, and fairly strong spectral features can be used for discrimination and quantification of Meloxicam in drug analysis. Frequency dependent refractive index of the drug was determined in a range of 0.2 THz–2.7 THz, where an almost constant index was observed with an average index of 1.75. Powder XRD, and solid-state Density Functional Theory (SS-DFT) calculations were utilized to determine the crystalline form of the Meloxicam sample in its enolic crystalline form. Single molecule DFT calculations were also performed in all four possible structures of Meloxicam. In addition, the capability of THz waves transmission through common packaging materials is demonstrated for possibility of future on-site analysis. The results suggest that drug analysis will be possible to perform not only at every stage of manufacturing without destruction but also directly at the shelf of a market after development of portable THz technologies.

1. Introduction

Application of THz waves have been diverse in many areas such as molecular spectroscopy [1], solid state physics [2,3], biology [4–6], imaging [7], and pharmaceuticals [8–11]. This frequency range covers collective vibrational or torsional modes in condensed-phase media, and rotational and vibrational modes of molecules. Thus, it is generally referred to as a spectral fingerprinting region similar to the mid-infrared range. The long wavelengths of THz radiation enables deeper penetration or transmission through many materials like skin, paper, plastic, many synthetics, textiles, etc. Thus, both identification and quantification of an Active Pharmaceutical Ingredients (API) of a drug becomes possible with its molecular fingerprints even if it is covered with the visibly opaque but THz transparent polymeric materials, such as blister packs. In addition, its low energy makes it non-invasive and safe and eliminates the worry of a change in drug morphology or form during the analysis/measurements. With these attractive features THz spectroscopy is recently gaining significant attention in characterization of drugs because of its potential use in identification (including discrimination of polymorphs) and quantification of API [9,10,12–15].

A recent study by Strachan et al. had shown that different solid-state forms of four different pharmaceutical compounds has very unique terahertz spectra in region of 0.1 THz–2.25 THz arising from the molecular nature of the chemicals and their crystallinity in each polymorph [9]. In addition, they successfully quantified all four chemicals and two different forms using partial least-squares analysis. In their study Ge et al. presented clear identification of 5 different polymorphs of furosemide using their spectral features between 0.2 THz and 1.6 THz [8]. In a study by Zeitler et al. the sensitivity of THz spectroscopy has been exploited in order to study temperature dependent polymorphism of Carbamazepine in the frequency range between 0.1 THz and 2.85 THz [16]. In a similar

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study by Sibik et al. crystallization and phase changes of paracetamol was successfully followed by terahertz [17].

In the pharmaceutical industry, one of the major efforts is to obtain drugs with optimum bioavailability, stability, and solubility besides maximizing its efficacy. Any change in molecular structure (even transitions within the polymorphic forms) prior to, during, or after manufacturing of the drug may result in an unwanted change in solubility, bioavailability, dissolution rate and possibly become a danger to human health [18]. In addition to a change in form of the API, the cocrystals formed during manufacturing could show unique solubility, dissolution rate, hydration stability, and bioavailability [19,20]. It has been shown that cocrystal formation processes could be investigated by using terahertz spectroscopy [21,22]. Therefore, characterization techniques must play a significant role in every part of the manufacturing processes. Common techniques used are X-ray diffractometry, differential scanning calorimetry, IR and Raman spectroscopies and solid state NMR [23–26]. In addition, Spatially Offset Raman spectroscopy (SORS) is a recently developed technique that is applicable on characterization of packaged pharmaceuticals, concealed drugs, and raw pharmaceutical materials non-invasively in their packages and containers [27,28]. Although it is a promising technique, it does have few restrictions. Since the laser employed in SORS is generally in the visible or NIR region the container or the protective cover thickness could be high enough and may hinder penetration of the laser. In addition, the technique may suffer from fluorescence signals emitted from API, packaging, capsule shell, tablet coating, or plastic container of the drug, and end up with noise suppressing the actual API signal. THz spectroscopy is an emerging and very promising new technique, which does not suffer from fluorescence contamination and has a greater penetration capability with its much longer wavelength. With the aforementioned advantages it is expected that THz methods will take its position as a complementary technique in the pharmaceutical industry in the near future.

The most common market form for pharmaceutical dosage of a drug is formed solid unit doses, commonly known as tablets, sold in blister packs. A tablet mainly contains the drug and inert fillers and binders (excipients) and are being analyzed before, during, and after manufacturing for content, quantity, and homogeneity. Prior to production, form of API and bulk pharmaceutical chemicals (excipients) are checked and confirmed. During the mass production, tablets are also tested for any change in the form of API when necessary. API should be dispersed in a tablet homogenously since controlled release for certain period may be required. Tablets may also be checked for having right amount of coating for controlled release of the drug or to protect for degradation due to harsh acidic conditions of the stomach, etc. In a recent study Lin et al. demonstrated the capability of THz spectroscopy to measure tablet coating thickness [29]. Furthermore, tablets are also analyzed for shelf life prior to marketing under simulated market conditions since an API may have limited stability and may change its form during storage. It would be necessary to characterize finished pharmaceuticals, if possible, right at the shelf on the market for further degradation due to the storage conditions in markets or pharmacies. Thus, THz spectroscopy appears to be a really good candidate to monitor tablets or drugs before, during, and after manufacturing processes for its morphology, homogeneity, and the tablet coating quality.

In this study we present optical properties of a pharmaceutically important drug called Meloxicam over the broad spectral range; 0.2 THz–20 THz. Meloxicam is an anti-inflammatory drug having analgesic and fever reducing effects and may also be used for arthritis treatment. In addition to absorption spectra and frequency dependent index of the pure Meloxicam, the spectra of the API were collected in PE matrix at various concentrations to simulate the excipients effect on the spectra, by which the capability of THz spectroscopy for quantitative characterization of Meloxicam was also investigated. Moreover, low temperature (77 K) spectra of the API is compared to room temperature spectra. Solid state DFT and single molecule DFT simulations are utilized to confirm/identify the crystal structure and determine the internal and phonon vibrational modes in the low frequency region of the spectrum. The measured spectra of Meloxicam are also a significant contribution to the collection of drug spectra currently being accumulated in the literature. Finally, THz spectra of Meloxicam samples were also collected through actual packaging materials to demonstrate the possibility of non-invasive and non-destructive analysis when the technology becomes readily portable.

2. Experimental

Meloxicam (PubChem CID 54677470, $C_{14}H_{13}N_3O_4S_2$) was obtained from Nobel R&D center in fine powder form and was used without further purification.[1] The packaging materials were obtained from the package of the commercialized drug named Melox (Nobel Pharma). High density polyethylene (PE) was obtained from Micro Powders Inc. with a particle size of ca. 10 μm. Samples were measured as pellets having 13 mm diameter. The mixture pellets at 5 wt%, 7.5 wt%, and 10 wt% concentrations in PE were prepared under 67 MPa (1 ton per 0.2 in^2) pressure for 20 s and the pure pellet were prepared under 67 MPa pressure for 10 min with mild vacuum. Since the sample and PE mixes well, no grinding or further processing was needed. No charge or static effect was noticed during mixing. In their study Wu et al. has shown effect of purging time prior to measurement mainly on the high frequency region [15]. We have also observed humidity effect on our pellets thus the sample and the reference pellets were measured at the same purging time (10 min) and flow rate in order to minimize this effect. The Meloxicam structure and its crystalline form in the solid sample was confirmed by ^{1}H NMR and Powder X-ray analysis, respectively. Low temperature (77 K) THz-TDS and THz-FTIR spectra of pure and PE mixture samples were collected with NIST THz-TDS and FTIR spectrometers.

2.1. Terahertz spectroscopy systems

Two THz time domain spectrometers (METU, TURKEY and NIST, USA), and two commercial FTIR spectrometers (Thermo Nicolet 6700, METU and Thermo Nicolet 550, NIST) were used to cover the spectral absorption range from 0.2 to 20 THz. The METU setup is similar to general TDS systems. The general characteristics of the METU THz-TDS setup and some of the differences are as follows. The light source is a mode-locked Ti:Sapphire oscillator laser (Coherent Mantis, 80 MHz, 80 fs pulsewidth, 800 nm central wavelength with ca. 80 nm bandwidth). In the generation arm, the pump beam was focused onto an LT-GaAs photoconductive antenna array (BATOP, iPCA-21-05-1000-800-h), where the excited electrons are accelerated by an applied bias voltage of 15 V at 8 kHz. The generated THz beam is guided by off-axis parabolic mirrors (OAPM) in 8F configuration, in which the light is collimated after the generation, focused onto a sample, collected and collimated with other off-axis mirrors, and then focused onto a 500 μm ⟨1 1 0⟩ ZnTe crystal (MTI corp.) for THz radiation mapping with 800 nm beam. THz beam pulse-shape is recorded with a combination of quarter waveplate (QWP), Wollaston prism (WP), balance photodiode (BPD), lock in amplifier, and a computer. The spectrometer set-up is shown in Scheme 1. THz pulse-shapes in the

[1] Certain commercial equipment or materials are identified in this paper to adequately specify the experimental procedures. In no case does the identification imply recommendation or endorsement by NIST, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.