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THz spectroscopy: An emerging technology for pharmaceutical development and pharmaceutical Process Analytical Technology (PAT) applications

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ABSTRACT

As an emerging technology, THz spectroscopy has gained increasing attention in the pharmaceutical area during the last decade. This attention is due to the fact that (1) it provides a promising alternative approach for in-depth understanding of both intermolecular interaction among pharmaceutical molecules and pharmaceutical product quality attributes; (2) it provides a promising alternative approach for enhanced process understanding of certain pharmaceutical manufacturing processes; and (3) the FDA pharmaceutical quality initiatives, most noticeably, the Process Analytical Technology (PAT) initiative. In this work, the current status and progress made so far on using THz spectroscopy for pharmaceutical development and pharmaceutical PAT applications are reviewed. In the spirit of demonstrating the utility of first principles modeling approach for addressing model validation challenge and reducing unnecessary model validation "burden" for facilitating THz pharmaceutical PAT applications, two scientific case studies based on published THz spectroscopy measurement results are created and discussed. Furthermore, other technical challenges and opportunities associated with adapting THz spectroscopy as a pharmaceutical PAT tool are highlighted.

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1. Introduction

Terahertz (THz) spectroscopy has been widely used to study the spectroscopic characteristics of a variety of materials [1,2], such as dielectrics, semiconductors, bio-molecules, liquids, and pharmaceutical products in the spectral region spanning from 0.1 to 10 THz. The THz pulses can be generated and detected using short-pulsed lasers with pulse widths ranging from ~100 down to ~10 femtosecond which is not present in conventional far-IR studies. During THz spectroscopic measurement, the transient electric field is measured, which determines the amplitude and phase of each of the spectral components that make up the pulse. Since the amplitude and phase are directly related to the absorption coefficient and index of refraction of the sample, the complex permittivity of the sample is obtained without having to carry out a Kramers–Kronig analysis [1]. The majority of crystalline solids have distinct and characteristic lattice vibrations within the THz frequency range, making THz spectroscopy a powerful analytical tool for probing the intermolecular interactions of molecular crystals. Due to its sensitivity to the intermolecular contacts impacted by the molecular packing arrangement in their crystal form, this technique shows promising for the analysis of pharmaceutical products throughout the drug development process [3,4]. Most noticeably, THz spectroscopy as an emerging technology has gained increasing attention in the area of pharmaceutical product and process understanding during the last decade.

FDA's pharmaceutical quality initiative [5] including Process Analytical Technology (PAT) [6] was highlighted in recently released FDA's strategic plan of advancing regulatory science [7]. "FDA will support the application of novel technologies to product development and innovative analytical approaches to improve product manufacturing and quality ... enabling development and evaluation of novel and improved manufacturing methods ... promoting two state-of-the-art manufacturing strategies—Process Analytical Technology, and Quality-by-Design approaches—for impact on manufacturers' ability to maintain consistent quality". In this work, current status and progress on using THz spectroscopy for pharmaceutical development and pharmaceutical PAT [6] applications are reviewed. Two scientific case studies were created based on published THz results to illustrate how to utilize first principles modeling approach to address model validation challenge and to reduce unnecessary model validation "burden", which might be helpful for facilitating THz pharmaceutical PAT applications. Furthermore, challenges and opportunities associated with adapting THz spectroscopy as a pharmaceutical PAT tool are highlighted.

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2. THz spectroscopy for pharmaceutical product characterization and pharmaceutical development

2.1. Crystalline pharmaceuticals, polymorph screening, and solid-state assessment

Solid-state property differences derived from the existence of alternate crystal forms could translate into measureable differences in properties of pharmaceutical importance. For example, solid-state, polymorphism and variations in the degree of crystallinity in a pharmaceutical substance may exhibit physicochemical differences that matter at therapeutic (such as dissolution, bioavailability, and area under curve (AUC)), manufacturing (choice of manufacturing route and processing equipment, etc.), marketing, and even legal levels. A book chapter by Brittain [8] described various methods for the characterization of polymorphs and solvates. X-ray diffraction remains as the established direct method for identifying and characterizing polymorphs. Vibration spectroscopic techniques have become increasingly important for monitoring crystallinity and polymorphism due to its advantages on speed, minimal sample preparation requirements, and adaptability for online analysis and control.

Compared to mid-infrared radiation, THz radiation has some unique advantages for pharmaceutical analysis, such as (1) its lower frequencies and longer wavelengths; (2) its sensitivity to vibrations of noncovalent bonds but not to those discrete bonds; (3) its longer wavelengths resulting in little scattering. Since the radiation energy that interacts with the pharmaceutical materials or dosage forms is less, the likelihood of damage to the pharmaceutical samples caused by the radiation will be lower. The vibrations of non-covalent bonds correspond to intermolecular vibrations or vibrations of large units in a molecule. Thus, THz spectroscopic techniques capture information on phonons in crystalline semiconductors and in molecular systems. This makes THz spectroscopic techniques suitable for identifying particular molecules. Pharmaceutical scientists can take advantage of this to locate physicochemical fingerprints of a particular pharmaceutical compound not previously available through Raman or IR spectroscopic techniques. The little scattering nature, when combined with low absorption in dry solids, makes THz radiation suitable for imaging. From a regulatory science perspective, single point measurement result always faces challenge of representativeness in the pharmaceutical setting. Therefore, imaging provides an alternate solution to address the concern of scale of scrutiny, since technically one can scan as many points as possible should the mechanical design of the imager allow. In this regard, information up to several millimeters beneath the surface of a dosage form can be probed in a nondestructive manner. Several studies have been reported to use THz spectroscopic technique for pharmaceutical process and development over the last several years, as summarized in Table 1 below.

2.2. Assessing weak interaction (inter-molecular vibrations) and intramolecular interaction

Applications of THz technology in probing the low-energy vibrational spectroscopy of materials have stimulated much interest due to the fact the vibrational spectroscopy plays a significant role in investigating the thermodynamic properties, structure of molecules, and medical application of THz light. Limwikrant et al. [17] reported their study on characterization of ofloxacin–oxalic complex (prepared by cogrinding method) by PXRD, NMR, and THz time-domain spectroscopy. Weak interaction between the two components such as van der Waals force and/or OH–π interaction occurred, was evidenced by IR and solid-state NMR spectra. These weak interactions could be detected in the THz range. The distinctive THz spectrum showed that the vibrational modes of the complex were different from those of pure components of ofloxacin and anhydrous oxalic acid. Low-frequency vibrations below 200 cm^{-1} of crystalline α,α-trehalose dehydrate were observed by far-infrared spectroscopy (FIRS) [18]. Spectral feature observed at 300 K agrees well with intramolecular normal vibrations obtained by density functional theory (DFT) calculations. Strong peaks observed at 67.7 and 75.9 cm^{-1} at 300 K were assigned to torsion modes of hydroxymethyl groups, hydrogen torsional motions of water molecules in trehalose dehydrate. Besides intramoelcular modes, intermolecular modes among four dihydate molecules in a unit cell and lattice modes due to periodic structure can be detected. Nagai et al. [19] measured the time-domain THz spectra of some chemical materials after being dipped in solvents or after application of spots of solvent, which provided direct evidence of inter-molecular vibrations. Their result shows that the solvents significantly affect inter-molecular vibrations. However, the interpretation of the results is phenomenological and rather complicated, and a further detailed study is needed. Shen et al. [20] discussed their experimental and theoretical studies of THz spectral features of caffeine and 3-acetylmorphine. It has been demonstrated that the two drugs have characteristic spectra in both the refractive indices and absorption, which can be used as fingerprint to identify the illicit drugs. Excellent agreement was obtained between the simulated spectra using density functional theory (DFT) and Hartree–Fork (HF) calculation and experimental spectra in the THz range.

2.3. Mapping chemical compositions and tablet density

Compared to the immediate release dosage form, the modified release or controlled release dosage form may have some additional quality attributes which are required to meet certain specifications before a specific dosage form with a specific strength can be granted for a marketing authorization by a pharmaceutical regulatory agency. For example, tablet coating layer thickness, controlled release rate, dissolution performance (for extended release dosage form), tablet density, composition, etc., are important quality attributes for a controlled release dosage form. THz spectroscopy has found applications for analyzing some of these pharmaceutical quality attributes.

Since many chemical compounds show specific frequency-dependent absorption in the THz range, a THz image can reveal the distribution of the spectral characteristics of the structures. Watanabe et al. [21] demonstrated the possibility for component analysis of chemical mixtures using THz spectroscopic imaging based on principal component analysis (PCA) and spectral data of several pure components. Their method could be helpful when searching for illegal drugs, poisons and devices of bioterrorism in various targets such as mail, packages, foods, and agricultural products using a database of THz spectra of chemicals. Palermo et al. [22] investigated procedures for generating multivariate prediction vectors for quantitative composition and density analysis of intact oral solid dosage forms using THz Pulsed Imaging (TPI) Spectroscopy. Quantitative frequency-domain composition calibration models were created for all crystalline components with R^2 value larger than 0.90. Combing two amorphous components into a single component variable for regression generated equally good predictions of crystalline components, although the effort to quantify individual amorphous component did not yield satisfactory result. A non-linear attenuation of time-domain spectra was observed as a function of compaction force, which can be correlated to compact density predictions with $R^2 = 0.948$. It was also found that refractive index spectra were sensitive to compact density ($R^2 = 0.937$), while the absorbance spectra were not. Therefore, this work suggested there is an advantage to using optical absorption for