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Terahertz pulsed spectroscopy and imaging for pharmaceutical applications: A review

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ABSTRACT

The terahertz region of the electromagnetic spectrum spans the frequency range between the infrared and the microwave. Traditionally the exploitation of this spectral region has been difficult owing to the lack of suitable source and detector. Over the last ten years or so, terahertz technology has advanced considerably with both terahertz pulsed spectroscopy (TPS) and terahertz pulsed imaging (TPI) instruments now commercially available. This review outlines some of the recent pharmaceutical applications of terahertz pulsed spectroscopy and imaging. The following application areas are highlighted: (1) discrimination and quantification of polymorphs/hydrates, (2) analysis of solid form transformation dynamics, (3) quantitative characterisation of tablet coatings: off-line and on-line, (4) tablet coating and dissolution, (5) spectroscopic imaging and chemical mapping. This review does not attempt to offer an exhaustive assessment of all anticipated pharmaceutical applications; rather it is an attempt to raise the awareness of the emerging opportunities and usefulness offered by this exciting technology.

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1. Introduction

The terahertz region of the electromagnetic spectrum spans the frequency range between the mid-infrared (IR) and the millimetre/microwave. The centre portion of the terahertz region (0.1–4 THz, 3.3–133 cm^{-1}) has a unique combination of properties in that: many amorphous pharmaceutical excipients are transparent or semitransparent to terahertz radiation whilst many crystalline materials have characteristic spectral features in terahertz region. Absorption features within the mid-IR region are dominated by intra-molecular vibrations of sample molecules thus mid-IR spectral features are "molecule fingerprints". In contrast, absorption features in terahertz region are dominated by inter-molecular vibrations, corresponding to motions associated with coherent, delocalized movements of large numbers of atoms and molecules (Walther et al., 2003; Shen et al., 2003; Day et al., 2006). Such collective phonon modes only exist in materials with periodic structure. In this sense, terahertz spectral features are "crystal fingerprints", and materials with identical molecular structures but different crystal forms (so-called crystal polymorphs) are expected to have different terahertz spectrum. Consequently terahertz spectroscopy is an excellent technique for characterizing the crystalline properties of solid materials, as the phonon lattice modes are probed directly.

Historically spectroscopy measurement in terahertz region has been difficult owing to the lack of suitable source and detector. The blackbody radiation source such as mercury arc lamps becomes increasingly inefficient when approaching terahertz frequency. Extremely sensitive cryogen cooled bolometer is thus necessary to detect this weak terahertz signal (Chantry, 1971; Ikeda et al., 2010). Furthermore, ambient conditions create considerable noise because the surrounding materials at room temperature radiate terahertz photons as well. Due to these difficulties, terahertz spectroscopy was not widely adopted in pharmaceutical analysis, despite of its excellent capability for effective polymorph discrimination.

The past 10 years have seen a revolution in terahertz systems (Ferguson and Zhang, 2002). Of particular significance is the development and commercialization of terahertz pulsed spectroscopy (TPS) and terahertz pulsed imaging (TPI) systems. The core technology is essentially the same between the spectroscopy set-up and the imaging set-up, as both utilize ultrafast femtosecond laser to generate and detect short pulses of broadband terahertz radiation. There are three main advantages of using pulsed terahertz radiation. Firstly, this technology directly measures the transient

Abbreviations: API, active pharmaceutical ingredients; ATR, attenuated total reflection; FDA, food and drug administration; MDT, mead dissolution time; PAT, process analytical technology; PLS, partial least square; FTIR, Fourier transform infrared; IR, infrared; TPI, terahertz pulsed imaging; TPS, terahertz pulsed spectroscopy.

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electric field, not simply the intensity of the terahertz radiation. This yields terahertz spectrum with far better sensitivity and dynamic range as compared with Fourier transform infrared (FTIR) method (Han et al., 2001). High-quality terahertz spectra are now routinely obtained in less than 20 ms without the need for cryogen cooled bolometer, making terahertz spectroscopy more easily and widely accessible. Secondly, because of this time-gated coherent detection technology used, the extraneous ambient noise (originated from the incoherent blackbody radiation from the sample and its surroundings) is minimised. This allows for the first time the use of terahertz spectroscopy for characterizing heated samples under extreme conditions (Cheville and Grischkowsky, 1995) and for *in situ* studies of phase transitions of pharmaceutical solids (Zeitler et al., 2006a,b). Thirdly the use of pulsed radiation and the associated coherent detection scheme preserves the time-gated phase information, upon which terahertz imaging has been developed for quantitatively characterizing inner structures of a sample non-destructively. The enormous inherent potential of the terahertz technology led to a rapid development of terahertz systems, and the availability of commercial terahertz products has opened up many exciting opportunities in pharmaceutical sector.

In-depth description of the terahertz theory, device and system has been provided by numerous earlier studies and reviews (Jepsen et al., 1996; Ferguson and Zhang, 2002; Schmuttenmaer, 2004; Chan et al., 2007; Jansen et al., 2010). Wallace et al. (2004, 2008) gave a brief introduction into early applications of terahertz technology in the pharmaceutical sciences. Excellent and detailed technical reviews on pharmaceutical applications of terahertz pulsed spectroscopy and imaging were published recently by Aaltonen et al. (2008), McGoverin et al. (2008), Zeitler et al. (2007b), Taday (2009). This article provides an overview of some recent developments and application highlights of terahertz spectroscopy and imaging in pharmaceutics and solid dosage forms.

2. Terahertz spectroscopy

2.1. Instrumentation, sample preparation and data analysis

Fig. 1 shows the schematic diagram of a typical transmission TPS instrument (Taday, 2004). Terahertz generation and detection was achieved using an ultrafast laser such as a Ti:sapphire laser. A beam splitter separated the laser light into two beams: an excitation beam and a probe beam. Terahertz pulses were generated by optical excitation of a biased photoconductive antenna (Auston, 1975) (Fig. 2). The terahertz pulses emitted from the antenna were collimated and focused onto the sample by an off-axis elliptic mirror. The transmitted terahertz pulses were then collected and focused using another off-axis elliptic mirror onto the surface of an unbiased photoconductive antenna for detection (Cheville and Grischkowsky, 1995).

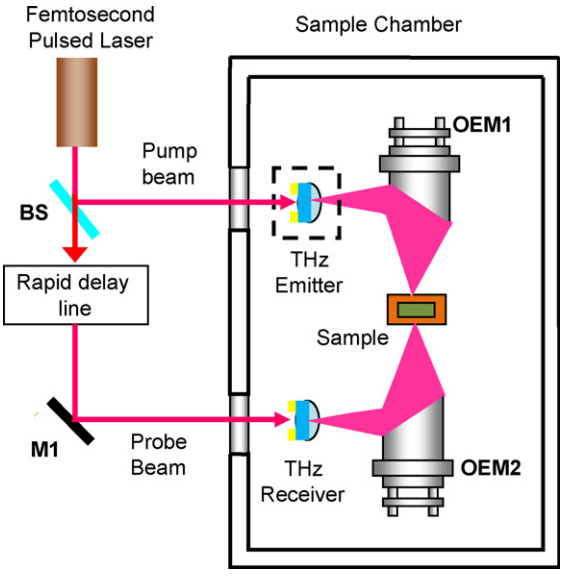

Fig. 1. Schematic diagram of a TPS instrument. BS: beam splitter; M1: metallic mirror; OEM1–OEM2: off-axis elliptic mirrors.

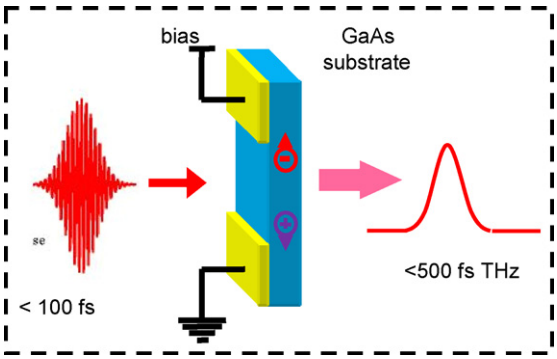

Fig. 2. Generation of broadband terahertz pulses in a gallium arsenide (GaAs) photoconductive antenna. Electron-hole pairs are excited in the GaAs crystal using an above-band gap femtosecond pulse (usually <100 fs pulses centered at a wavelength of 780 nm, with a 78 MHz repetition rate). These photoexcited carriers are accelerated by an applied electric field. The physical separation of the electrons and holes forms a macroscopic space-charge field oriented opposite to the biasing field, and thus, the externally applied field is screened. The fast temporal change in electric field produces a transient current, which generates a pulse of electromagnetic radiation in the terahertz frequency range.

In TPS measurements, the transient terahertz electric field was recorded as a function of the time-delay between the terahertz pulse and the probe pulse using a variable delay stage. The spectral resolution of the measurement was determined by the overall time-delay scanned. Most commercial instruments are able to provide a spectral resolution of better than 1 cm^{-1} by scanning a time-delay distance of greater than 5 mm. A waveguide configuration could be used to obtain sharper spectral signature (Laman et al., 2008). Usually the sample chamber is either purged with dry nitrogen gas or evacuated throughout the measurement to reduce the effects of water vapor absorption.

For quantitative spectral measurement, the time-resolved electric field of terahertz pulses before and after propagating through the sample was measured. The terahertz pulse transmitted through the sample is modified by the dispersion and absorption of the media under examination. Both the refractive index $n(\nu)$, and the absorption coefficient $\alpha(\nu)$, can be extracted,

$$\frac{E_S(\nu)}{E_R(\nu)} = T(n)\exp\left[-\alpha(\nu)d + \frac{j2\pi n(\nu)d}{c}\right]$$

where d is the thickness of the sample, ν the frequency of the radiation, c the speed of light in vacuum, and $T(n)$ is a factor which accounts for refection losses at the sample surfaces (Fischer et al., 2005).

To date, most terahertz spectroscopy measurements have been performed in transmission configuration such as the one shown in Fig. 1. In order to obtain high-quality and reliable terahertz spectra, the sample material is usually mixed with high-density polyethylene (PE) fine powder, and then compressed into a pellet for acquiring terahertz spectrum. PE is a good binding material and is nearly transparent with a frequency-independent refraction index of 1.53 in terahertz region (Walther et al., 2003). A circular pellet (13 mm diameter, about 3 mm thickness, compressed under 2-tons) containing 40 mg sample powder and 360 mg PE powder usually provides acceptable terahertz spectrum for most pharmaceutical powder samples. Pellet with a thickness of larger than

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