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Review

Terahertz pulsed imaging as an advanced characterisation tool for film coatings—A review

Miriam Haaser[a,b,c], Keith C. Gordon[d], Clare J. Strachan[e,*], Thomas Rades[f]

[a] School of Pharmacy, University of Otago, P.O. Box 56, Dunedin, New Zealand
[b] Cavendish Laboratory, University of Cambridge, Cambridge CB3 0HE, UK
[c] TeraView Ltd., St. John's Innovation Park, Cambridge CB4 0WS, UK
[d] Department of Chemistry, MacDiarmid Institute for Advanced Materials and Nanotechnology, University of Otago, Dunedin, New Zealand
[e] Division of Pharmaceutical Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland
[f] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

Solid dosage forms are the pharmaceutical drug delivery systems of choice for oral drug delivery. These solid dosage forms are often coated to modify the physico-chemical properties of the active pharmaceutical ingredients (APIs), in particular to alter release kinetics. Since the product performance of coated dosage forms is a function of their critical coating attributes, including coating thickness, uniformity, and density, more advanced quality control techniques than weight gain are required. A recently introduced non-destructive method to quantitatively characterise coating quality is terahertz pulsed imaging (TPI). The ability of terahertz radiation to penetrate many pharmaceutical materials enables structural features of coated solid dosage forms to be probed at depth, which is not readily achievable with other established imaging techniques, e.g. near-infrared (NIR) and Raman spectroscopy. In this review TPI is introduced and various applications of the technique in pharmaceutical coating analysis are discussed. These include evaluation of coating thickness, uniformity, surface morphology, density, defects and buried structures as well as correlation between TPI measurements and drug release performance, coating process monitoring and scale up. Furthermore, challenges and limitations of the technique are discussed.

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1. Introduction

Over recent decades, with the development of photoconductive semiconductor antenna technology (Auston, 1975; Fattinger and Grischkowsky, 1989) and advances in ultrafast laser technology (femtosecond lasers) (Tonouchi, 2007; Saeedkia and Safavi-Naeini, 2008), the so-called 'terahertz gap' of the electromagnetic spectrum, spanning between the mid-infrared and microwave region (also called far-infrared region), became accessible at room

* Corresponding author at: Division of Pharmaceutical Technology, Faculty of Pharmacy, University of Helsinki, Viikinkaari 5E, P.O. Box 56, FI-00014, Finland. Tel.: +358 9 191 59736.
E-mail address: clare.strachan@helsinki.fi (C.J. Strachan).

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temperature. This enabled the development of commercially usable terahertz pulsed spectroscopy (TPS, also known as terahertz time-domain spectroscopy), and terahertz pulsed imaging (TPI) systems. The current instrument set-ups used for pharmaceutical analysis cover a spectral range of 2–130 cm^{-1} (60 GHz–4 THz) (Taday and Newnham, 2004).

TPS is a non-destructive technique. The terahertz radiation interacts with vibrational modes of non-covalent bonds. In contrast to mid and near-infrared (IR) spectroscopy, where absorption features are primarily related to intra-molecular vibrations and the information obtained is mainly chemical (molecular fingerprints), the lower-energy absorption features in the terahertz region include oscillations of large units in a molecule, inter-molecular bond vibrations and phonon lattice modes (Shen et al., 2003; Walther et al., 2003; Day et al., 2006). As phonon modes are strongly correlated to periodic structures found in crystalline materials, terahertz absorption features of crystalline materials can be defined as "crystal fingerprints". Consequently, the ability to probe lattice dynamics directly provides information on crystalline properties of complex solid materials, which makes terahertz spectroscopy an excellent tool to analyse solid-state pharmaceuticals properties (Zeitler and Gladden, 2008). The sensitivity to changes in the periodic structure of materials is comparable with that of X-ray powder diffraction (XRPD). Low wavenumber Raman spectroscopy provides complementary information about lattice modes and the potential of this approach has been demonstrated (Hédoux et al., 2009, 2011; Hubert et al., 2011). Due to the nature of terahertz radiation, terahertz spectroscopy does not heat the sample or induce photochemical reactions. Furthermore, since it uses much longer wavelengths than Raman or near-IR spectroscopy, terahertz spectroscopy can be less prone to signal scattering by particles (Wallace et al., 2004; Shen et al., 2008).

Applications of TPS in the pharmaceutical sciences include polymorph discrimination and characterisation (Taday et al., 2003; Strachan et al., 2004; Zeitler et al., 2006b), discrimination between different hydrate forms of APIs (Zeitler et al., 2006a; Balbuena et al., 2008), API and polymorph quantification in pharmaceuticals (Taday, 2004; Strachan et al., 2005), and detection and quantification of phase transitions in solid samples (Zeitler et al., 2005; Nguyen et al., 2007; Zeitler et al., 2007b). Other fields of applications also include astrophysics (Siegel, 2006, 2007), security/explosives (Kemp et al., 2003; Shen et al., 2005a), chemical recognition of substances (Fischer et al., 2005), bio-medical sciences (Wallace et al., 2004; Pickwell et al., 2005), and medical imaging (Fitzgerald et al., 2006; Ashworth et al., 2009; Pickwell-MacPherson and Wallace, 2009). In addition, interpretation of the spectral features observed by terahertz spectroscopy as well as assigning them is a very active and ongoing field of research (Wu et al., 2007), but a detailed description on interpretation of the TPS absorption spectra of crystalline solids would exceed the scope of this review. More information on this interesting research sector has been provided for example by Chen et al. (2004), Zeitler et al. (2005), Day et al. (2006), Allis et al. (2006), Jepsen and Clark (2007), Aaltonen et al. (2008), and Li et al. (2010).

Besides the application of terahertz spectroscopy for the determination of solid-state pharmaceutical properties, time-resolved analysis of reflections of terahertz radiation propagating through pharmaceutical solid-state dosage forms allows their structure in the depth direction to be explored. In contrast to crystalline materials, the absence of periodic structures in amorphous materials results in an absence of absorption peaks due to phonon modes, and many are transparent or semi-transparent to terahertz radiation. As most pharmaceutical excipients used for tablet coating, i.e. most film coating materials, are amorphous, the terahertz pulse can penetrate through the sample allowing deep probing of the sample structure using TPI (Wallace et al., 2004; Zeitler et al., 2006c), whilst other spectroscopic techniques, such as NIR or Raman spectroscopy, fail to provide information from below the sample surface (Chan et al., 2003; Reich, 2005). Detailed and very good reviews on applications of TPS and TPI in the pharmaceutical sector were recently published by Zeitler et al. (2007a), McGoverin et al. (2008), Taday (2009), Shen (2011), and Wu and Khan (2012). This review offers an overview of recent pharmaceutical applications of TPI, highlighting the developments of terahertz pulsed imaging as an advanced characterisation tool for film coatings.

2. Terahertz pulsed imaging (TPI)

2.1. Core technology, instrumentation and data collection

The core module technology used in the TPI system is essentially that of the TPS system. Briefly, generation of broadband terahertz pulses is achieved by focussing ultrafast femtosecond (fs) laser pulses on a biased semiconductor substrate such as gallium arsenide (GaAs). The incident laser pulse excites the electrons of the semiconductor substrate generating electron–hole pairs. These photocarriers enable a transient current to flow across the photoconductive switch, which is then closed (acting like a radiating dipole antenna) giving rise to an ultrashort terahertz pulse (electromagnetic radiation in the terahertz frequency range) (Auston, 1975) (Fig. 1). Detection of terahertz radiation is essentially the reverse method to its generation using a solid-state receiver at room temperature (Fattinger and Grischkowsky, 1989). Together with a very high signal-to-noise ratio of $>10^5$, this time-gated coherent technique provides both electric field amplitude and phase information. Hence, both the spectral absorption coefficient and the refractive index (RI) of a sample can be extracted directly.

Terahertz spectrometers are fairly compact and thus portable. The acquisition time for a high quality spectrum is well below 1 min, providing a spectral resolution of 1 cm^{-1}. Nevertheless, a spectrum can be obtained in only a couple of milliseconds if necessary. This allows time-critical applications, including in-line process control of the tablet film coating process. Further information on the various different methods to generate and detect terahertz radiation is beyond the scope of this review and can be found in very good technical reviews on this topic (Beard et al., 2002; Schmuttenmaer, 2004; Jepsen et al., 2011).

In contrast to most TPS systems, where the terahertz radiation is detected on the opposite side of a sample after propagating through it, TPI systems are set up in reflection mode (terahertz emitter and receiver are on the same side of the sample and reflections from within the sample are detected). In modern TPI systems, the modification of optical fibres for both the pump and probe beam allows the probe (terahertz emitter and receiver) to be placed in a separate imaging unit, where for example a six-axis robotic arm presents the sample orthogonal and at the right distance to the terahertz radiation allowing mapping over the entire sample surface (Fig. 2).

Before the introduction of a six-axis robotic arm only investigations of flat surfaces (Shen et al., 2005b) and raster scanning across a small square section of solid pharmaceutical formulations (Wallace et al., 2004) were carried out. With the introduction of a programmable robotic arm, by guiding the pump and the probe beam into optical fibres to link the spectroscopy unit with the imaging unit in TPI instruments, the generation of 2D and 3D images of solid dosage forms in their entirety became accessible. Fig. 2 shows a schematic diagram of a terahertz imaging set-up using such a sixth axis robotic arm which is employed to ensure that the sample surface is always at a normal angle, and at the right distance to the terahertz emitter/detector. The imaging unit in TPI instruments such as the TPI Imaga2000 system (TeraView, Cambridge,