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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.

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).

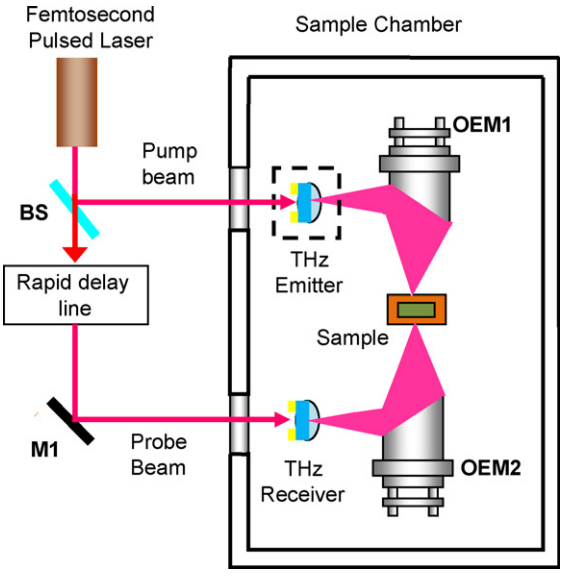

Fig. 1. Schematic diagram of a TPS instrument. BS: beam splitter; M1: metallic mirror; OEM1–OEM2: off-axis elliptic mirrors.

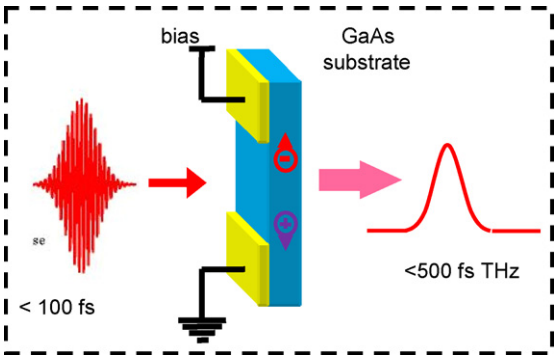

Fig. 2. Generation of broadband terahertz pulses in a gallium arsenide (GaAs) photoconductive antenna. Electron-hole pairs are excited in the GaAs crystal using an above-band gap femtosecond pulse (usually <100 fs pulses centered at a wavelength of 780 nm, with a 78 MHz repetition rate). These photoexcited 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

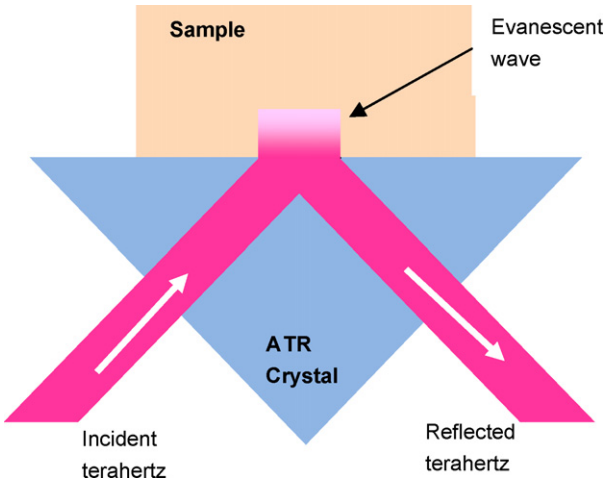

Fig. 3. Schematic illustration of the terahertz ATR sampling technique. When a beam of terahertz light irradiates the crystal–sample interface (from below) at an angle greater than the critical angle, total internal reflection occurs at the crystal–sample interface. Such total internal reflection forms the evanescent wave that extends into and interacts with the sample material. Note that total internal reflection occurs only when the refractive index of the crystal is larger than that of the sample under study. For terahertz ATR spectroscopy, silicon crystal is most widely used because it has very low dispersion and transmission losses in terahertz region with a refractive index of 3.42, which is larger than that of most pharmaceutical solids.

3 mm has the advantage of preventing the acquisition of multiple reflections of the terahertz pulse, which would lead to etaloning artefact in the recorded spectra (Strachan et al., 2004; Zeitler et al., 2005).

An alternative sampling technique for terahertz spectroscopy is to use the attenuated total reflection (ATR) configuration (Newnham and Taday (2008)). As shown in Fig. 3, the key part of the ATR configuration is a crystal with a very high refractive index. Terahertz ATR measurements can easily be made by simply placing a small amount of powder or liquid sample onto the crystal. Using a silicon-crystal based terahertz ATR system, Newnham and Taday (2008) measured a number of pharmaceutical solid samples, and they found that terahertz ATR spectral signatures agree with those measured using a standard transmission TPS system. TPS in ATR configuration could be a powerful tool for polymorphs screening, as it requires small amounts of sample—typically 1 mg for solids, with no sample preparation necessary, and the material can be recovered afterwards. However, the penetration depth of terahertz radiation into the sample varies with the wavelength and the incident angle of the terahertz beam. Extensive calibration might be necessary if quantitative terahertz spectral measurements are needed.

Generally speaking, TPS transmission measurement provides reliable and quantitative terahertz spectra whilst terahertz ATR measurement is most suitable for the rapid screening of many samples. In addition, terahertz spectrum can be measured using a reflection configuration (Pickwell and Wallace, 2006; Shen et al., 2008), which can be used to study opaque samples such as big solid dosage forms or tablets in packages.

As compared with near- and mid-IR spectroscopy, terahertz spectroscopy utilizes much longer wavelength and is therefore less prone to scattering by micrometer-sized particles. Nevertheless, the effects of scattering on TPS measurements cannot be ignored, particularly for granulated materials with particle size comparable to the wavelength of the terahertz radiation. In a recent food and drug administration (FDA) study, Wu et al. (2007) measured terahertz spectra of a number of granulated pharmaceutical materials with grain size comparable to terahertz wavelength. It was found that the particle scattering becomes significant at higher terahertz frequencies. Therefore, for reliable terahertz spectroscopic measurements, it is important to consider scattering effects and, wherever possible, to minimize such effects by using finely milled powder and by compressing powder into the form of pellet. Alternatively, good quality terahertz spectrum can also be obtained by averaging multiple measurements over a large sample area (Shen et al., 2008), although the measurement time would be significantly increased.

2.2. Polymorphism and crystallization

Crystal polymorphs are defined as substances that are chemically identical but exist in more than one crystal form, and generally differ in physicochemical properties. The polymorphism is a common phenomenon among pharmaceuticals. It has been shown that about 80% of active pharmaceutical ingredients (API) have polymorphs (Grunenberg et al., 1996). The impact of polymorphs has been widely reported in the literatures, affecting such properties as dissolution rate, solubility, bioavailability and manufacturability (Brittain, 2007). The detection of polymorphs in drug discovery and manufacturing process is very important for assuring sufficient quality of the API. To date, a wide spectrum of analytical techniques has been used extensively to characterize polymorphs, and this includes crystallographic, spectroscopic, microscopic, and thermal techniques. Powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), IR spectroscopy, Raman spectroscopy and solid state NMR measurement are generally applied for polymorph analysis of APIs (Zeitler et al., 2007b). Although most of polymorphs are identifiable by these analytical techniques, there is not one method that could address the issue of high throughput polymorph screening or could quickly and conveniently confirm the polymorphic state of drugs while in storage or during manufacturing. A quick, simple, and versatile technique for investigating the different polymorphic forms would be advantageous.

As aforementioned, terahertz spectroscopy directly probes the lattice phonon modes thus is ideal for characterizing crystalline pharmaceuticals. The first application of TPS for polymorph discrimination was reported by Taday et al. (2003) where two different polymorphs of ranitidine hydrochloride could be readily discriminated using their terahertz spectra. This stimulated a lot of interest in using TPS for characterizing crystalline properties of different drugs. Strachan et al. (2004) studied a number of pharmaceutical compounds in polymorphic, liquid crystalline and amorphous forms. They found that the different polymorphic forms of carbamazepine and enalapril maleate exhibit distinct terahertz absorbance spectra. In contrast to crystalline indomethacin and fenoprofen calcium, amorphous indomethacin and liquid crystalline fenoprofen calcium show no absorption modes. These findings provide further evidence that terahertz pulsed spectroscopy is wellsuited for distinguishing crystallinity differences in pharmaceutical compounds. Zeitler et al. (2006a) investigated sulfathiazole, a drug with five known polymorphic forms. It was found that all five known polymorphs of sulfathiazole were readily distinguished by their terahertz spectra (Fig. 4). Furthermore, it was shown that, by using terahertz spectroscopy, mixtures of the different sulfathiazole polymorphs could be detected easily; whereas this was not possible for certain of its forms by any spectroscopic technique in the mid- or near-IR (Zeitler et al., 2006a). This work is of particular significance as it clearly demonstrated that TPS possessed some advantages over other techniques.

Terahertz spectroscopy has been shown to have a number of advantages: good quality spectra can be acquired in much less than a second; as the terahertz power used is orders of magnitude lower than that used in other techniques such as Raman spectroscopy, no sample heating effects are observed; as the photon energy of terahertz radiation is one million times smaller than that of X-ray and one thousand times smaller than that of UV light, no photochemical

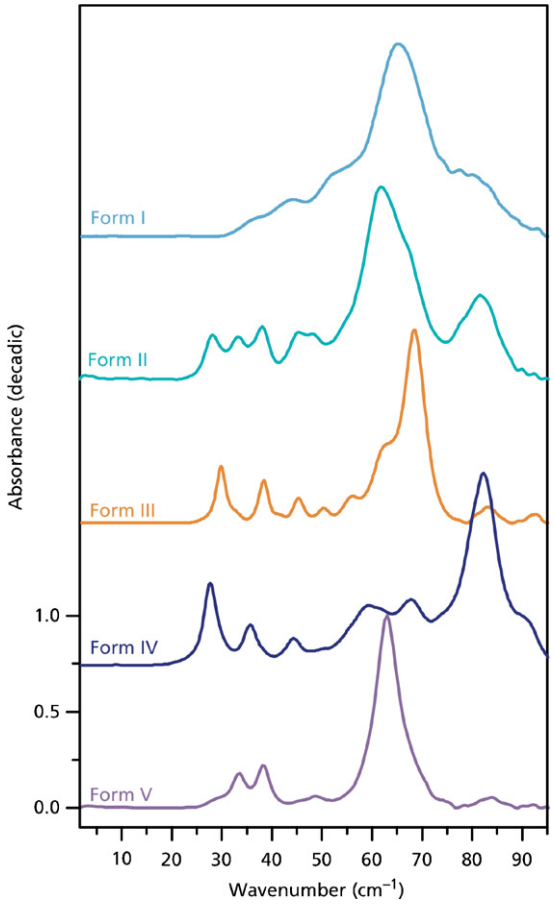

Fig. 4. Terahertz spectra of the five polymorphic forms of sulfathiazole. Spectra are vertically offset, background corrected, and normalized for clarity. Reproduced from Zeitler et al., 2006a.

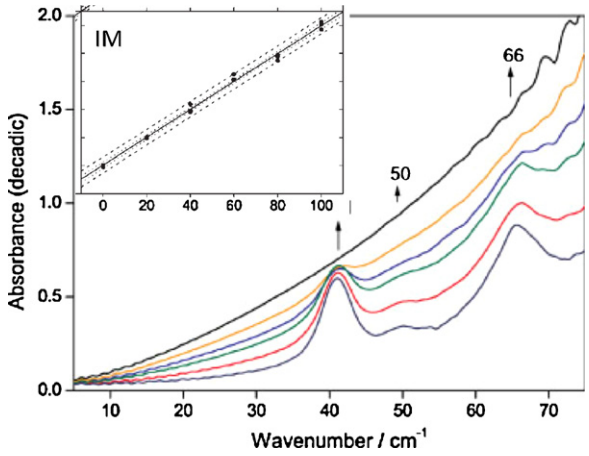

Fig. 5. Terahertz spectra of binary mixtures of indomethacin amorphous and crystalline forms (20% intervals, 0–100% crystalline form). The arrows indicate spectral changes as the amorphous form concentration decreases and the crystalline form concentration increases. Each spectrum is the average of three spectra (from three independent samples) that were smoothed using the Savitzky–Golay algorithm to remove etaloning artefacts (13 smoothing points). The inset shows the predicted versus the actual concentration in the range of 0–100%. Reproduced from Strachan et al., 2005).

effects are expected at the terahertz region. This makes terahertz spectroscopy particularly suitable for rapid polymorph discrimination in both drug discovery and manufacture stages. For example, Ge et al. (2009) applied TPS to analyze the five forms of the modified furosemide and one commercial product. Each form shows a distinct terahertz absorption feature, making it possible to distinguish the five different modifications of furosemide. Chakkittakandy et al. (2010) observed distinct terahertz spectra of the β and δ polymorphs of mannitol. They were able to show that, for freeze-dried mannitol, changes in the way the material is frozen can result in the formation of different polymorphs or a mixture of polymorphs. The recent work by Ikeda et al. (2010) also suggests that terahertz spectroscopy has unique power in the elucidation of molecular interactions within a crystal lattice and can play a more important role in physicochemical research as a general tool for polymorphic determination.

2.3. Anhydrous and hydrated pharmaceutical materials

Not only can different polymorphic forms of drugs be distinguished by their terahertz spectra, but it is also possible to differentiate between different hydrate forms. Lactose, one of the most commonly used excipients in the pharmaceutical industry, forms at least three different hydrates: α-monohydrate, α-anhydrate, and β-anhydrate form. These three hydrate forms exhibit terahertz spectra with distinct features (Zeitler et al., 2006b). In addition, it was found that TPS is able to discriminate theophylline monohydrate and its anhydrous forms (Upadhya et al., 2006; Balbuena et al., 2008), and the anhydrous and monohydrated caffeine molecules and crystals (Balbuena et al., 2008). In a separate study, Liu et al. (2007a) showed that pseudopolymorphs, anhydrous and hydrated forms of theophylline, ampicillin, D-glucose and caffeine are distinguishable using terahertz spectroscopy. Recently terahertz spectroscopy was used to characterize ceftazidime and its generic versions (Kawase et al., 2009). Terahertz results show small, but significant difference in the states of ceftazidime hydrate between the original and generic versions. It was conclude that TPS can be used to evaluate the stability of medicines as well as to monitor/control their quality. Table 1 summarizes some of the crystalline pharmaceuticals that have been studied using TPS.

2.4. Pharmaceuticals quantification

Other studies have investigated the application of terahertz spectroscopy for quantitatively analyzing pharmaceuticals. It was shown that the APIs (acetylsalicylic acid and paracetamol) could be quantified in the presence of excipients (lactose and cellulose) from the terahertz absorption spectra using a multivariate partial-least-squares (PLS) calibration model (Taday, 2004). Strachan et al. (2005) studied the ability of TPS to quantify polymorphic forms in binary mixtures (Fig. 5). The limits of detection achieved for carbamazepine form III, enalapril maleate form II and crystalline fenoprofen calcium were 1.23% w/w, 0.69% w/w, and 2.69% w/w, respectively. In a similar study, Nishikiori et al. (2008) observed different absorption bands for DL-tartaric acid and its enantiomers (L- and D-tartaric acid). Using PLS method they were able to quantify L-tartaric acid in L- and DL-tartaric acid mixture. Wu et al. (2008) demonstrated the feasibility of integrating terahertz spectroscopy and chemometrics for the purpose of quantifying pharmaceutical tablet concentrations. Otsuka et al. (2010) reported that the two forms of mefenamic acid have distinct terahertz spectra, and this allows the amount of form I and II to be quantified using a chemometric model based on PLS method. Despite these progresses, the validation of TPS for quantifying the amount of APIs in real world solid dosage forms has yet to be published.

2.5. Solid phase transformation

Solid phase transformations proceed directly from one solid-state form to the other, without any intermediate liquid phases.

Table 1
Terahertz spectral signatures of some crystalline pharmaceuticals.

Sample	Form/state	Signature (cm^{-1})	Reference	Sample	Form/state	Signature (cm^{-1})	Reference
Apo-ranitidine		32,43,62,73	Taday et al. (2003)	Aspirin		62,78,83,96,111,123	Taday (2004) Laman et al. (2008)
Ampicillin	Anhydrate	23,54,69,93	Liu et al. (2007a)	Caffeine	Anhydrate	26, 42	Liu et al. (2007a)
	Trihydrate	42,55,66,77,87			Hydrate	39,50,76	Shen et al. (2010)
3-acetylmorphine		33,47,64	Shen et al. (2010)	Ephedrine		26,32,45,55,76,92	Hakey et al. (2009)
Benzoic	Pure	37,72,78,94,103,125	Jepsen and Clark (2007)	Enalapril maleate	Form I	23, 39, 69	
Acid	3-Hydroxy	30,32,69,75,79	Laman et al. (2008)		Form II	20, 27, 57	Strachan et al. (2004)
	4-Hydroxy	66,71,82,107					
Carbamazepine	Form III	41,60,91,109,122		Lactose	Pure	19,51,95	
	Form I	31, 52	Zeitler et al. (2006b)		α-Anhydrate	33,41,65,80,91,96	Zeitler et al. (2006b)
	Dihydrate	62, 71,101	Ikeda et al. (2010)		β-Anhydrate	40,45,62,74,80,89	Taday (2004)
	Form II	33, 113			Monohydrate	18,41,47,62,89	
Allantoin	4K	46,57,81,85	Upadhya et al. (2003)	Fenoprofen calcium		17, 27, 52,~66	Strachan et al. (2004)
Uric Acid	4K	42,48,83		Indomethacin		41, 50, 66	
Fructose	B-D-Fructose	62,75,98,106	Walther et al. (2003)	Zantac		40,48,58,66,76,83,93	Taday et al. (2003)
Furosemide	Form I	37, 50	Ge et al. (2009)	Sulfathiazole	Form I	65	Zeitler et al. (2006a)
	Form II	34, 49			Form II	61, 82	
	Form III	37, 51			Form III	45, 50, 83, 92	
	Form IV	37			Form IV	28, 36, 44	
	Form V	34			Form V	63, 84	
Glucose	D-Glucose	42, 48, 70	Upadhya et al. (2003)	Organic	L-Ascorbic acid	36,50,60,68,78,97,109	
	L-Glucose	48, 71	Liu and Zhang (2006)	Acids	Citric acid	57, 69, 77, 99, 114	Newnham and Taday (2008)
	Monohydrate	61, 66, 82	Walther et al. (2003)		L-tartaric acid	36, 62, 87, 101, 111	
Mefenamic acid	Form I	54, 176	Otsuka et al. (2010)	Piroxicam	Form I	69,73,93	Zeitler et al. (2006b)
	Form II	41, 162			Monohydrate	41,49,56,62,70,80,84	
Ofloxacin	Pure	36	Limwikrant et al. (2009)	Paracetamol	2-acetamino phen	45,55,68,77,82	Taday (2004)
	Oxalic acid complex	20			3-acetamino phen	36,52,62,72,85	
	Glutaric acid complex	33, 42			4-acetamino phen	48,70,93	
	Malonic acid complex	39		Sucrose	10K	45,57,63,90,102	Walther et al. (2003)Shen et al. (2008)
Polymer	Dimer	145,170,185,200	Balbuena et al. (2008)	Sugar alcohols	D-mannitol	38,81,106,113	Newnham and Taday (2008)
	Tetramer	100, 230, 275			D-sorbitol	40,47,61,69,77,102	
	Pentamer	60,105,155,170,195			Xylitol	55,62,84,93,100	
Ranitidine HCl	Form I	32,42,59,68,73,85,92	Taday et al. (2003)	Salicylic acid		41,68,75,81,85	Laman et al. (2008)
	Form II	38,47,62,75,80,92	Wallace et al. (2004)	Thymine		70,80,95,105,108	Jepsen and Clark (2007)
Tartaric acid	L-Tartaric acid	36,62,78	Nishikiori et al. (2008)	Tolbutamide	Form I	83,103	Ikeda et al. (2010)
	D-Tartaric acid	36, 62			Form II	47,80	
	DL-Tartaric acid	56, 80			Form III	37,53,73,90	
Theophylline	Form I	37,47,77,115,125	Upadhya et al. (2006)	Vitamins	Pyridoxine	27,47,82,92,103	Newnham and Taday (2008)
	Form II	33,55,127,132	Zeitler et al. (2006b)		Riboflavin	34,39,59,64,76,86	
	Monohydrate	57,90,133			Thiamine hydrochloride	37,59,91,97,108	

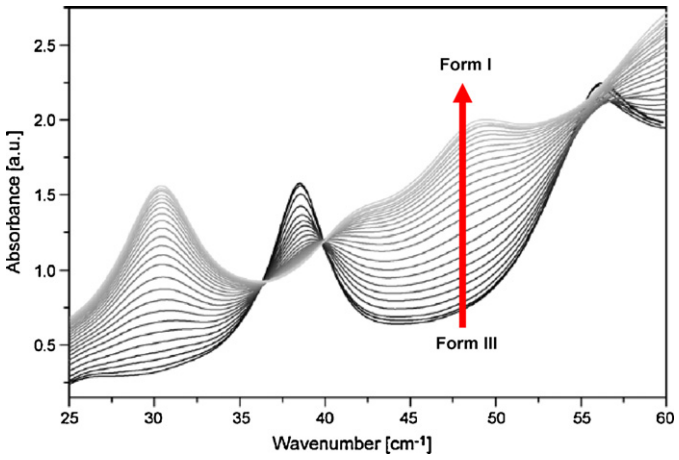

Fig. 6. TPS spectra of the isothermal solid–solid transformation from CBZ form 3 (black) to 1 (light grey) at 438 K. The spectra were taken in 5 min intervals until complete conversion.
Reproduced from Zeitler et al., 2005.

These transformations are significantly influenced by environmental conditions, including temperature, pressure and relative humidity. Solid-state transformations may occur during any stage of pharmaceutical processing and upon storage of a solid dosage form. Early detection and quantification of these transformations during the manufacture of solid dosage form is important since the physical form of an API can significantly influence its processing behaviour, including powder flow and compressibility, and biopharmaceutical properties such as solubility, dissolution rate and bioavailability (Aaltonen et al., 2008; Heinz et al., 2009a,b).

The first study to use temperature-dependent TPS for pharmaceutical analysis was reported by Zeitler et al. (2005), where the reversible solid-state transformation of carbamazepine form III to form I was characterized (Fig. 6). In a further study, Zeitler et al. (2007c) studied *in situ* the relaxation and crystallization of amorphous carbamazepine using a variable temperature TPS. Even though terahertz spectra of disordered materials in the glassy state exhibit no distinct spectral features, the crystallization leads to distinct spectral features allowing the crystallization and the subsequent polymorphic phase transition at higher temperature to be studied in detail. In other studies, variable-temperature TPS was also used to study the five known polymorphs of sulfathiazole and their solid-state conversions upon heating (Zeitler et al., 2006a,b) and to characterize solid state polymorphic transformations in theophylline (Upadhya et al., 2006). Liu and Zhang (2006) used TPS to characterize the dehydration kinetics of polycrystalline hydrates. The dehydration kinetics was found to obey the contracting area equation of the solid-state reaction. These studies demonstrated that TPS is an effective new tool to characterize the kinetics of solid phase transformation.

Nguyen et al. (2007) applied TPS for quantitative monitoring of dynamic process of cocrystal formation (formed mechanochemically by grinding together phenazine and mesaconic acid). Limwikrant et al. (2009) used TPS for the characterization of ofloxacin–oxalic acid complex. The distinctive terahertz spectra showed that the vibrational modes of the complex are different from those of the starting materials, suggesting that TPS is an alternative tool to evaluate complex formation through weak interactions.

The photon energy of terahertz radiation is in the range of a few meV (one thousand times smaller than that of UV light and one million times smaller than that of X-ray). This makes TPS intrinsically safe to use because no photochemical effect is expected at such a low energy level. However, the precise modeling and assignment of the corresponding phonon vibration modes with such a low energy is extremely challenging, because one has to take into consideration all the weak yet complex intermolecular interactions in crystalline materials. Consequently a detailed interpretation of the spectral changes that occurred during conversion of the respective API is rather difficult. Nevertheless, a number of groups have begun to attempt to interpret/assign the spectral features observed in the terahertz region (Day et al., 2006; Allis et al., 2006; Saito et al., 2006; Gordon et al., 2007; Jepsen and Clark, 2007; Balbuena et al., 2008; Hakey et al., 2009; Heinz et al., 2009a; Hooper et al., 2009; Li et al., 2010). This is currently a very active and exciting research area. With the improvements in computer power and the further development of coding that can readily handle more complex systems, such as unit cells and many-molecule problems, a full understanding of the spectral changes observed in variable temperature TPS will be possible. This in turn will have a significant impact in improving the ultimate understanding of pharmaceutical materials, formulations and processes.

3. Terahertz imaging

3.1. Imaging set-up, sample preparation and data analysis

The ability to generate terahertz radiation from a point source coupled with the fact that many pharmaceutical excipients are semitransparent in this region has resulted in the development of imaging systems capable of nondestructive, three-dimensional investigations of solid dosage forms (Zeitler et al., 2007a; Shen and Taday, 2008). The core technology is essentially the same between the spectroscopy set-up (Fig. 1) and the imaging set-up (Fig. 7). Terahertz radiation is generated by pumping a biased photoconductive antenna with an ultrashort laser pulse from a Ti:sapphire laser. The emitted terahertz pulse is collected, collimated, and then focused onto a sample under test. The reflected and backscattered terahertz pulse is then collected and focused onto an unbiased photoconductive antenna for the laser-gated terahertz detection.

In a TPI measurement, the terahertz waveform is taken at many points mapped over the surface of a sample, and at each pixel terahertz waveform is recorded as a function of optical time delay. Thus TPI provides three-dimensional information: the *x*- and *y*-axis describe vertical and horizontal dimensions of the sample and the *z*-axis represents the time-delay (depth) dimension. Note that a reflection configuration is more appropriate for terahertz imaging. This not only allows thick sample, which may be opaque to

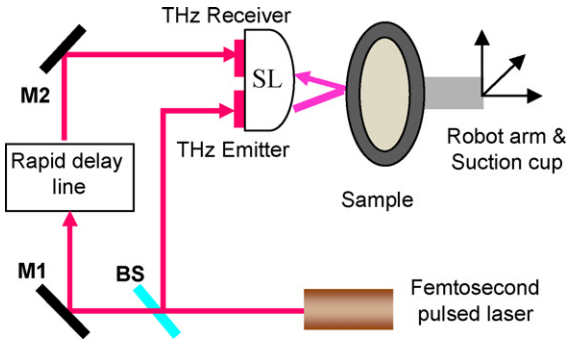

Fig. 7. Schematic diagram of a terahertz pulsed imaging (TPI) system. SL: silicon lens system; BS: Beam Splitter; M1–M2: metallic mirrors. Both terahertz emitter and detector were directly attached to a specially designed silicon lens system, thus avoiding the requirement of nitrogen purging (water vapour absorption was minimised owing to the shorter distance between the terahertz lens and the sample). In addition, most pharmaceutical tablets have curved surfaces therefore a six-axis robot system was used to move the sample according to a pre-generated surface model. In this way, during TPI measurement the sample is always at the terahertz focus position with sample surface always perpendicular to the terahertz probe.

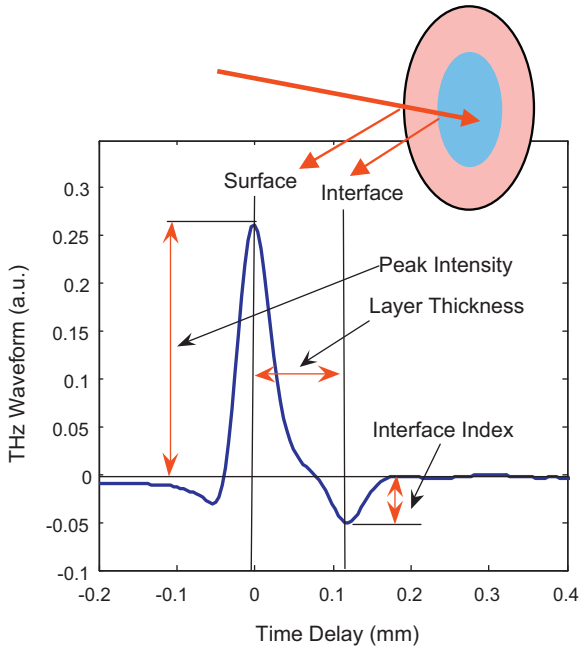

Fig. 8. A typical terahertz waveform measured for a single-layer coated tablet. The coating layer thickness is directly calculated as the time delay between the surface reflection and interface reflection (divided by the refractive index of the coating). Other terahertz parameters such as peak intensity (related to the refractive index of the coating, i.e., surface hardness or density) and interface index (related to the changes of the refractive index at the coating/core interface) can also be extracted simultaneously from the same terahertz waveform. These physico-chemical properties of the coating are closely correlated to the tablet dissolution performance. The insert shows schematically how terahertz pulses were reflected from the surface and interface of a tablet.

terahertz radiation, to be imaged (Wallace et al., 2008), but more importantly, this allows the use of the time-of-flight capabilities of the technique.

No sample preparation is required, and most pharmaceutical solid dosage forms with common shapes and surface curvatures can be imaged using the commercial TPI product (Zeitler et al., 2007a). By measuring the arrival time difference of terahertz pulses (reflected from the surface of a sample and from the inner structures of a sample), the coating thickness can be determined directly (Fig. 8). This is advantageous over near-IR spectroscopy method, which requires a calibration model thus is an indirect method (Cogdill et al., 2007; Maurer and Leuenberger, 2009). Maps of the coating thicknesses of dosage forms can be obtained by calculating the thickness from the time delay at each point. This can be done not only for the top coating layer but also for any subsequent sub-surface layers within the products.

Due to the coherent nature of the terahertz generation/detection method, the technique has a very high signal-to-noise ratio, and it can be applied at room-temperature. As the macroscopic structures on the surface of tablet samples are much smaller than the wavelength, scattering is not significant (Wallace et al., 2004). The lateral resolution is limited by the wavelength and the depth resolution is limited by the pulse duration. For most pharmaceutical products, the achieved spatial resolution is 150–250 μm in lateral and 30–40 μm in axial direction (Zeitler et al., 2007a; Shen and Taday, 2008).

3.2. Coating thickness measurement

Despite the ongoing development of more sophisticated solid drug delivery systems, the tablet remains the single most important solid dosage form that is used to administer drugs to a patient. It is the dosage form of choice because it combines reproducible drug dosage, high stability during storage, and can be economically produced (Wagh et al., 2009). Conveniently, a number of techniques are available to control the release kinetics of the drug that is embedded in the tablet: coating layers can be applied that dissolve rapidly at elevated pH while being insoluble in the acidic conditions of the stomach (enteric coatings), slowly eroding polymer coatings can be used to modify the drug release rate (Cole, 1995). The development of advanced tablet coatings requires quality control techniques that are ideally nondestructive, give spatially resolved information, and have a strong specificity to the properties that limit the quality of the tablet once it is administered to the patient. TPI has demonstrated to be a strong potential to address those needs of the industry (Zeitler et al., 2007b; Wallace et al., 2008).

In a proof-of-principle work, Fitzgerald et al. (2005) studied coated pharmaceutical tablets using a table-top terahertz imaging system. It was found that the coating thickness of the sugar-coated tablets could be determined quantitatively and non-destructively. The success of this work has led to the further development of a commercial TPI instrument for fully automated acquisition of terahertz imaging data of tablet (TPI imaga 2000, TeraView Ltd.). The first example of how TPI can be used to study film-coated tablets was demonstrated by Zeitler et al. (2007a). It was found that coating thickness and uniformity could be readily obtained for a wide range of commercially available pharmaceutical dosage forms such as film-coated tablets, controlled release tablets and soft gelatin capsules (Zeitler et al., 2007a). In other studies, TPI has been used for the analysis of coating thickness and uniformity of sustained-release tablets (Ho et al., 2007), and for investigating the coating characteristics of push–pull osmotic systems (Malaterre et al., 2009).

Because the TPI measurement covers the whole tablet surface, aspects of coating defects along with their site, depth and size were identified with virtual terahertz cross-sections. As an example, Fig. 9 reveals the intra-tablet variation of coating layer thickness (the coating thickness around the central band was thinner than that on the tablet top and bottom surfaces), with Fig. 10 showing the inter-tablet variation of the coating layer thickness of eight tablets with the same coating time (weight gain). In development of film coating technology, weight gain data during coating is used and it is assumed that a uniform distribution of the film exists over the whole surface of the tablet and across the whole batch of tablets. The TPI results, validated by the destructive optical microscope analysis, demonstrated that this is not always an appropriate assumption (Ho et al., 2007).

3.3. Coating process monitoring: off-line and in-line

In other studies, TPI was used for the monitoring of the coating process of film-coated tablets, and its results were compared with near-IR (NIR) spectroscopy (Cogdill et al., 2007) or NIR imaging (Maurer and Leuenberger, 2009). Samples taken from a pan coater at different time points were analyzed by both methods. TPI measurements provided direct coating thickness value/distribution over the whole sample surface, this way also showing inter- and intra-tablet differences (Cogdill et al., 2007; Maurer and Leuenberger, 2009). NIR imaging also gave information about inter- and intra-tablet coating layer differences, but as an indirect method, real layer thickness value was not obtained. It was not possible to obtain NIR imaging information about the tablet centre-band either, owing to the strong curvature. As both TPI and NIR methods were able to visualize the growth of the coating layer and to detect small defects in the coating non-destructively, they may prove useful in a PAT context as valuable tools to monitor the coating process. Another potential imaging method for coating analysis is optical coherence tomography (Zhong et al., 2009;

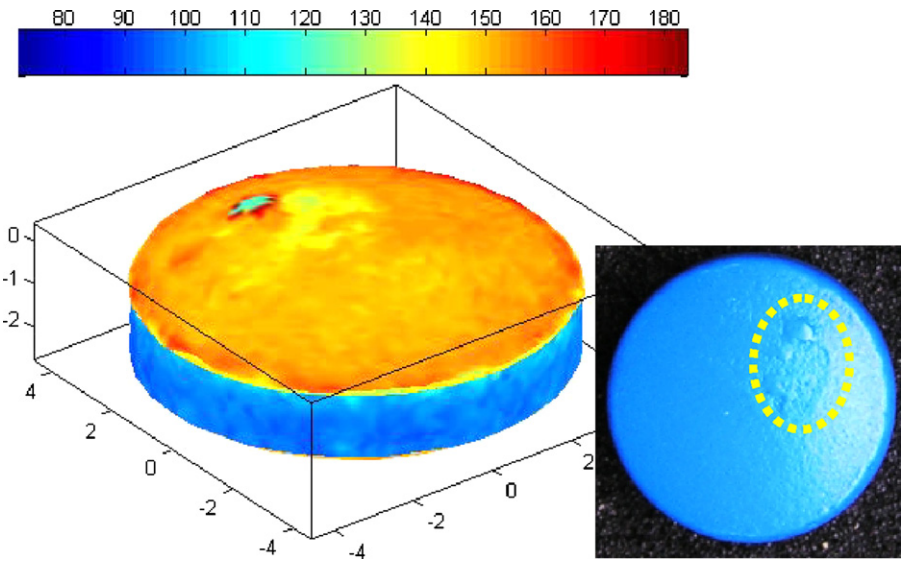

Fig. 9. Three-dimensional TPI false color image showing the coating thickness map of the two tablet surfaces and the central band. Color represents coating thickness, and the scale is in μm. The scales in the *x*, *y* and *z* directions are in mm. The coating layer thickness around the central band is much thinner than that on the surfaces of the tablet (Ho et al., 2007). The insert shows the optical photograph of the same tablet where the defect areas are highlighted by a yellow ellipse. The optical photographs are not necessarily oriented in the same fashion as the TPI maps and may require rotation to match. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Mauritz et al., 2010). NIR imaging proved to be better at thinner coating layers and had a higher spatial resolution whereas TPI had the clear advantage that it provided direct thickness values, even for very thick coating layers (Zhong et al., 2011).

In a recent study, May et al. (2010) demonstrated for the first time how terahertz pulsed technology can be used to quantitatively measure the coating thickness of randomly moving tablets in a production scale pan coater using an in-line terahertz sensor. The acquisition time to produce a coating thickness map of an entire tablet can be as much as 60 min using the reference high resolution TPI method. In contrast the in-line sensor is able to assess the thickness of a single tablet in less than 9 ms during process conditions without interfering with the coating process. Direct thickness measurement of film coatings is achieved with sub-micron resolution without the need for any prior chemometric calibration models. Fig. 11 shows a typical plot of coating thickness measured by the in-line process sensor as a function of coating time over 300 min coating process. The ability to measure the coating thickness distribution in the coating pan *in situ* cannot be achieved using any of the currently available near-infrared or Raman sensor technology, as each measurement point acquired with these techniques inherently represents the temporal and spatial average over a large number of tablets compared to the single tablet measurements made using the terahertz sensor. In principle this development allows terahertz sensors to make their way from the development laboratory to the manufacturing floor. This exciting new sensor technology could have considerable impact in process understanding, process analytical technology (PAT) and quality-by-design (QbD) developments of film coating processes, although more research is required to assess the full potential of this new sensor technology.

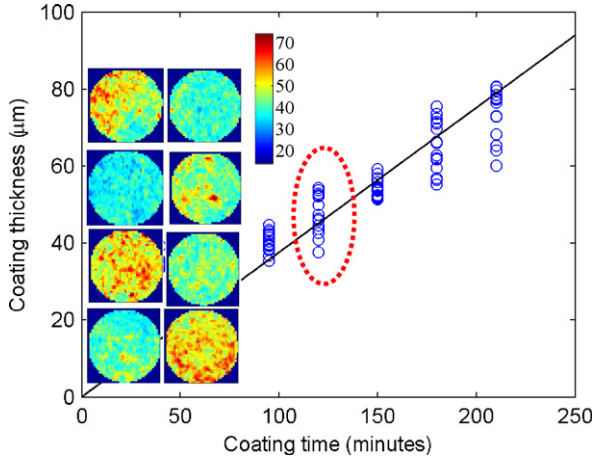

Fig. 10. The averaged coating thickness of each individual tablet against the coating time. The inset shows the coating thickness map (in μm) of eight tablets with the same coating time of 120-min. A large tablet-to-tablet variation of coating thickness is visible.

3.4. Tablet density and hardness analysis

Powder compaction is a unit operation employed frequently in pharmaceuticals. During compaction, movements take place within the powder bed and interactions occur between the powder and tooling (i.e., the die wall and punch faces). As a result, density variations are induced in the volume of the tablet, which may affect its physical and mechanical properties. Density variations within solid oral dosage forms are important because they may lead to differences in dissolution or mechanical response during post-compaction operations, packaging, storage or use (Sinka et al., 2004).

The ability to quantitatively measure density maps of a tablet using TPI was investigated by Palermo et al. (2008). As shown in Fig. 12, it was possible to quantify the effect of compaction force on the refractive index of the solid oral dosage forms using TPI spectroscopy. A multivariate calibration was performed that was able to predict the density of compacted mixtures of four excipients. Using this chemometric model, the density distribution over the surface of flat tablets was predicted from the TPI maps. In a further study, May et al. (2009) applied TPI for the analysis of the "hardness" (crushing strength) of pharmaceutical tablets. Radically symmetric spatial distributions in tablet density due to the shape of the punch used in the tablet manufacture were observed. They found a strong correlation between TPI results and those from diametric compression tests as well as finite element

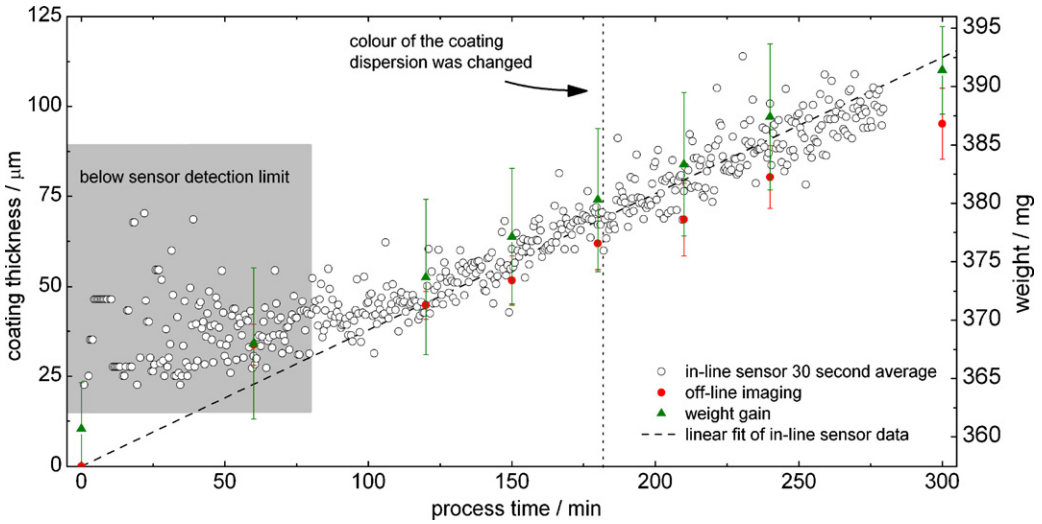

Fig. 11. Coating thickness measured by the in-line process sensor as a function of process time (open circles). For clarity the measurements are subdivided into bins of 30 s duration and the data points correspond to the average thickness during each 30 s bin. The black dashed line indicates the trend line based on the linear fit over all in-line data points above the sensor detection limit which was indicated in the figure by the shaded region. The closed red circles correspond to the coating thickness as measured by off-line TPI. Each data point represents the average coating thickness over both surfaces of six tablets removed from the coating pan. The closed green triangles indicate the average weight gain of 20 tablets. Before 80 min process time the coating thickness was below the minimum resolution. After 180 min process time (indicated by the vertical dotted line) the color of the coating dispersion was changed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
Reproduced from May et al., 2010.

analysis (FEA) simulations. It was concluded that TPI has advantage over the traditional diametric compression test (Hoag et al., 2008), which is destructive in nature and provides no spatial distribution information of the tensile strength of the tablet under study. All these results suggest that TPI is suitable for non-destructive monitoring and analysis of pharmaceutical manufacturing processes.

In a related study, Juuti et al. (2009) investigated the surface roughness and bulk properties of starch acetate tablets. The time delay of the terahertz pulses transmitted through a tablet was found to be correlated with the porosity of the tablet across a range of compression pressure (in a different study, the transmission terahertz spectra of porous media were also studied by Tuononen et al. (2010)). This suggests that TPI could also be useful for characterizing tablet bulk properties nondestructively.

3.5. Dissolution profiles

One of the most common practices in the pharmaceutical industry is the determination of dissolution profile in drug tablets. This is currently performed using a dissolution apparatus and often requires a long time analysis. Efforts have been made to implement lesser cost and time-consuming methods in order to predict dissolution performance of tablets (Zannikosm et al., 1991). As the TPI experiment is non-destructive, it was possible to perform dissolution testing on the same tablet samples that were used for the coating thickness determination.

In a study by Spencer et al. (2008), the mean dissolution time (MDT) was found to correlate with the coating thickness of enteric-layer coated tablets. Ho et al. (2008) investigated the potential of using terahertz data to predict the dissolution performance of sustained-release tablets from lab- and pilot-scale batches. Weight gain, the traditional non-destructive indicator for coating quality in the dry-state, failed to reflect the functional performance of the product. Conversely terahertz parameters could be correlated with the actual product performance. The correlation between coating thickness and MDT was very clear and much stronger than in the study by Spencer et al. (2008). In addition, the authors highlighted that changes in coating density is also a good indicator of the dissolution performance of the coated tablet.

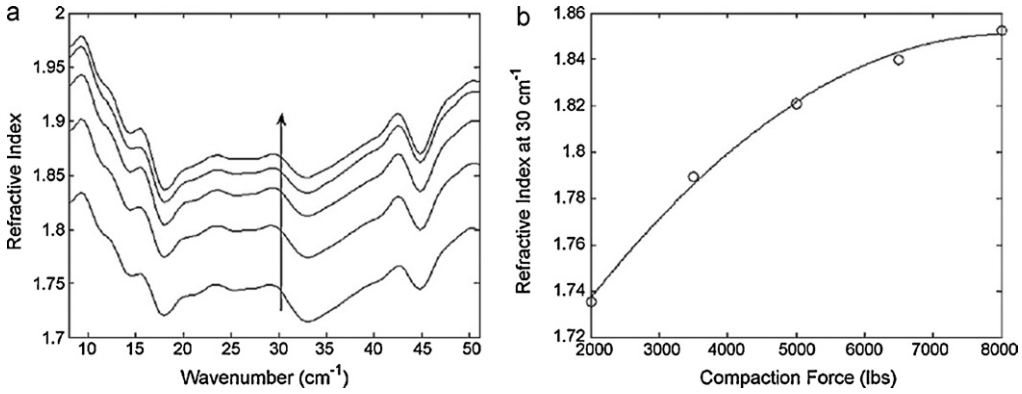

Fig. 12. Effect of compaction force (2000, 3500, 5000, 6500 and 8000 lbs) on the mean refractive index spectra of all compacts. The arrow indicates the direction of increasing force.
Reproduced from Palermo et al., 2008.

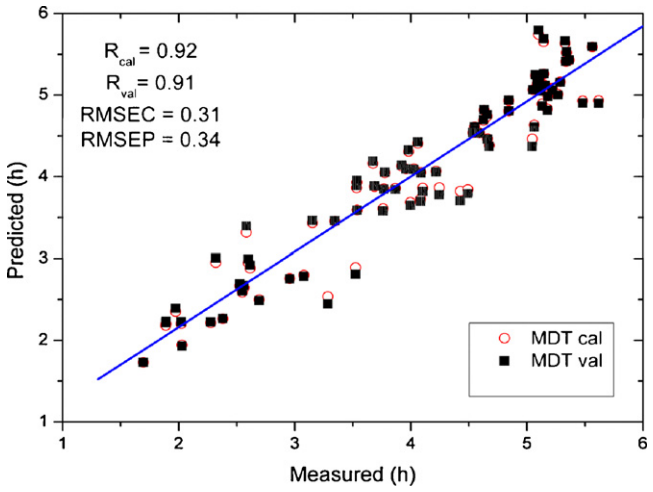

Fig. 13. Measured versus predicted MDT from the nonscaled PLS model. Both calibration and validation data points are presented here.
Reproduced from Ho et al., 2009b

Malaterre et al. (2009) applied TPI to investigate the coating characteristics of push–pull osmotic systems. It was concluded that the internal physical alterations impacting the drug release kinetics were detectable by using the terahertz time-domain signal. In a further study by Ho et al. (2009b), the whole terahertz waveform, rather than the derived coating thickness and coating density, was used to predict the tablet dissolution performance. Using a two-component PLS model, it was possible to predict the MDT of the corresponding *in vitro* dissolution whilst the tablets were still intact (Fig. 13). This multivariate method is particularly useful to predict the dissolution performance of tablet with thin coatings, as currently the thinnest coating thickness that can be precisely determined by TPI is around 40 μm.

For the case of coating uniformity, Ho et al. (2010) investigated a batch of round, biconvex tablets. It was observed that the coating thickness around the tablet central band domain was significantly smaller, with lower film coating density and higher surface roughness when compared to that on the top and bottom domain on biconvex tablets. Results from conventional dissolution testing confirmed that drug release from the central band was faster than that from the top and bottom surfaces (Ho et al., 2010). In a related study (Ho et al., 2009c), TPI was employed for the first time to non-destructively investigate the effects of film coating thickness, drug layer uniformity and the effect of curing on *in vitro* drug release from sustained-release coated pellets. The results from the TPI analysis indicated that there were significant differences in film coating thickness, surface roughness and drug layer uniformity, and these results were confirmed with scanning electron microscope (SEM) analysis. In contrast to previous TPI studies (Spencer et al., 2008; Ho et al., 2008), the terahertz parameters derived from the film coating were not indicative of the subsequent drug release performance from the pellets investigated (Ho et al., 2009c). This might be due to the predominant drug release mechanism was not diffusion through the film coating structure (as it was the case with the sustained-release coated tablets).

Tablet coating is one of many unit operations involved in the manufacturing of pharmaceutical solid dosage forms. The accurate detection and monitoring of weak spots in the film coating unit operation is a pressing issue, vital to the success of the product and process development. Using terahertz parameters the tablet central band was identified as the film coating 'weak spot' on round, biconvex tablets (Ho et al., 2010). This suggests that TPI, as a non-destructive analytical technique, has potential to be employed as a process analytical tool to probe film coating weak spots during film coating development and to assess its effect on the subsequent dissolution performance. The speed and ease of TPI mapping may make it an attractive replacement for wet dissolution testing both in product development and eventually for process analysis. However, it was acknowledged that the delayed-release system was very complex and the coating thickness was only one factor contributing to the dissolution performance amongst others.

3.6. Process scale-up and solvent diffusion in polymer matrices

Dissolution testing is currently the bench-mark for assessing the success of a scale-up operation in the film coating process. In order to evaluate the applicability of TPI for understanding of process scale-up, Ho et al. (2009a) analyzed one-hundred and ninety sustained-release tablets that were sampled during the scale-up operation of a film coating process from the lab- to the pilot-scale. After TPI analysis, dissolution testing was performed on the same tablets, and the results from TPI analysis and dissolution testing were correlated. It was shown that both process signatures, namely the coating thickness and coating density, were more informative on the product quality as compared with the amount of polymer applied (weight gain). Whilst the coating layer thickness was the governing factor of the subsequent dissolution behaviour for monitoring a specific film coating unit operation, differences in the film coating density showed a more prominent effect on dissolution during process scale-up. With these measurements it was possible to detect the *in vitro* performance differences between the pilot- and lab-scale. The results of this study not only demonstrate that TPI can be used for the non-destructive evaluation of the film thickness, but also suggest that the information obtained from the terahertz imaging experiment contains much more quantitative information on the physico-chemical properties of the coating that can be used to assess its quality.

Portieri et al. (2007) have investigated the hydration process of hydroxypropyl methyl cellulose (HPMC) based coatings matrices. HPMC is a polymer commonly used in the production of tablets to control the drug release. The mechanism of release is governed by swelling of the surface of the tablet when in contact with water. A layer of hydrogel is formed by polymer hydration and chain relaxation. This layer represents a barrier that retards processes of further water uptake and of drug release. Since the kinetics of drug release must match a proper dosage form, detailed information about dynamics of gel formation is needed. As shown in Fig. 14, the shape and integrity of the gel layer formed after adding a drop of 10 μl water onto a HPMC tablet can be mapped using TPI technique. In other study, Obradovic et al. (2007) demonstrated how TPI can be used to study solvent diffusion into a polymer matrix, a process that is key to the characterization of sustained release matrix tablets.

3.7. Chemical mapping

Chemical mapping is an exciting new analytical advance that provides comprehensive information characterising complex heterogeneous samples. The basis of chemical mapping is the acquisition of a three-dimensional data set where two axes describe vertical and horizontal spatial dimensions, and the third axis represents the spectral frequency dimension. In TPI measurement, the electric field of terahertz radiation was recorded as a function of time. Spectral information was obtained by Fourier transforming time-domain terahertz waveform into frequency domain. The absorption coefficient, $\alpha(\nu)$, and the refractive index, $n(\nu)$, were then calculated for each pixel as (Shen and Taday, 2008):

$$\sqrt{\varepsilon(\nu)} = n(\nu) + j\frac{\alpha(\nu)c}{4\pi\nu} = \frac{1 - E_S(\nu)/E_M(\nu)}{1 + E_S(\nu)/E_M(\nu)}$$

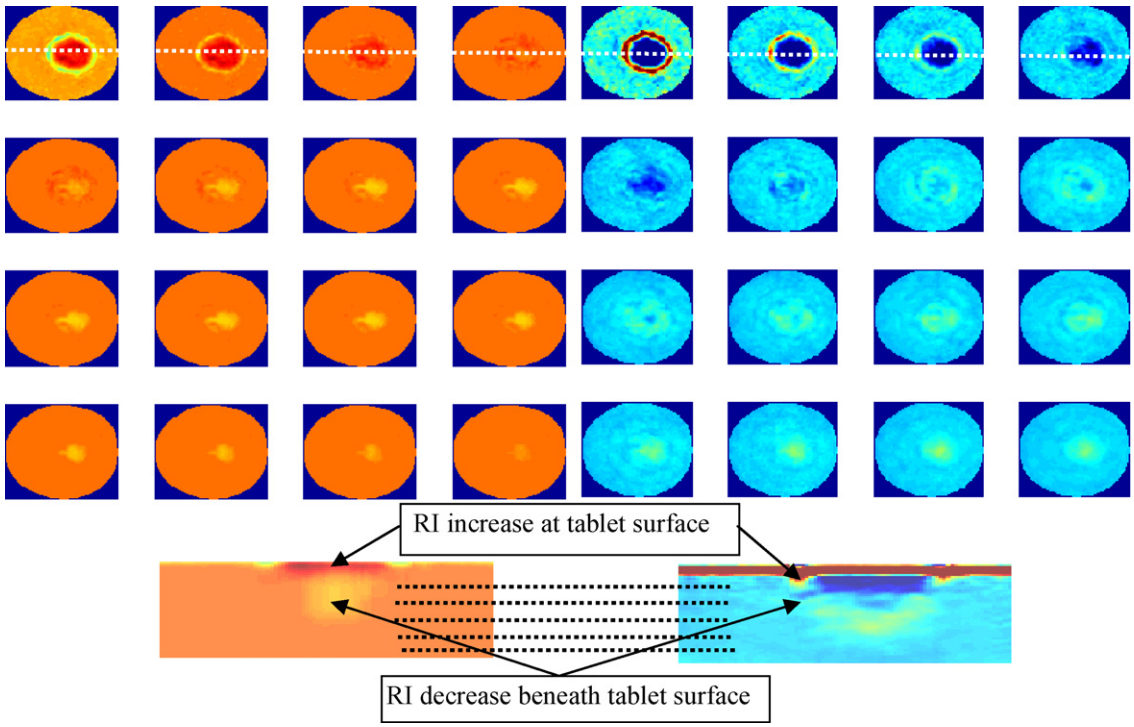

Fig. 14. Cross-sectional refractive index (left) and the change of refractive index (right) maps at various depths of 30 μm interval (top) and at $x = 0$ mm (bottom). Three distinct regions are clearly visible: a high-density shell (gel layer) at sample surface; a low-density porous region (water channels) below the surface; and a relatively high-density region into the tablet core. White dotted line in top figure is where $x = 0$ mm, and black dotted lines in bottom figure represent various depths where cross-section maps were sliced.

where $E_S(\nu)$ and $E_M(\nu)$ are the Fourier transform of the terahertz waveforms measured for a sample and a reference mirror. The refractive index $n(\nu)$ was used for mapping the tablet density (Palermo et al., 2008) and hardness (May et al., 2009) whilst the absorption spectra $\alpha(\nu)$ provides means for chemical mapping of pharmaceutical solid dosage forms.

In a proof of principle study, Shen et al. (2005a,b) recorded the chemical distribution of lactose and sucrose over the surface of a sample pellet. It was possible to distinguish the chemicals and determine the spatial distribution of the composition within the sample. In a further study, Cogdill et al. (2006) used a more advanced signal processing technique for terahertz chemical mapping in real pharmaceutical tablets rather than a polyethylene matrix. The tablets were direct compressed mixtures of MCC, lactose and theophylline. By using the terahertz maps of a set of calibration samples, it was possible to build different multivariate models for quantitative image analysis. The quantitative models were tested using tablets made of two spatially separated segments of different mixing ratios. Other studies (Fischer et al., 2005; Walther et al., 2010) also demonstrated chemical sensing and imaging capability of terahertz imaging using a transmission configuration.

In the near-IR and mid-IR range, FTIR and Raman spectroscopy have been successfully developed for chemical mapping (Lewis et al., 1995; Koening et al., 2001; Clarke et al., 2001). However, many pharmaceutical tablet coatings are opaque to IR light, owing to either strong absorption or scattering. Therefore conventional IR technique is mostly suitable for mapping out the surface distributions of chemicals, and thus is a two-dimensional chemical mapping technique. In addition, near-IR and mid-IR imaging technology would not be able to discriminate between different pharmaceutical polymorphs. Terahertz radiation, on the other hand, can penetrate deep into a tablet sample and is also capable of polymorph discrimination. Therefore in principle, TPI provides the necessary penetration capability and spectral specificity for non-destructive chemical mapping in a three-dimensional matrix. Using a model sample that contained well-confined domains of lactose and tartaric acid, Shen et al. (2005b) demonstrated how the spectral signatures of the materials could indeed be extracted non-destructively at depth. A time-partitioned Fourier transform of the reflected terahertz waveform with a fixed window width was then employed to produce depth-resolved spectral components of the pulse (Shen et al., 2005b; Shen and Taday, 2008). There are many potential applications for this experiment in the context of pharmaceutical dosage forms: for example, investigating the spatial distribution of different polymorphic forms in a dosage form as a result of compaction or coating, moisture uptake during storage of a tablet, drug stability over storage time in the final product etc. (Zeitler and Gladden, 2009). On the other hand, the model sample used (Shen et al., 2005b; Shen and Taday, 2008) was made of polyethylene, which is almost transparent to terahertz radiation. For a realistic pharmaceutical tablet, the spectral resolution at depth will be influenced strongly by scattering and refraction caused by the tablet matrix. Further work will be necessary to develop a robust method to routinely perform three-dimensional chemical mapping experiments. In addition, most commercial TPI system provides a lateral resolution of around 200 μm and better resolution is necessary in order to resolve small polymorph/hydrate particles/domains within pharmaceutical dosage forms.

4. Summary and outlook

Knowledge of the solid-state properties is one of the key issues in understanding the performance of drugs. Recent developments in terahertz spectroscopy and imaging technology offer new strategies for examining pharmaceutical solid dosage forms. TPS and TPI have been shown to be effective for discrimination and quantifica-

tion of polymorphs/hydrates, analysis of solid form transformation dynamics, quantitative characterisation of tablets and tablet coatings, and spectroscopic imaging and chemical mapping. Terahertz in-line sensor for direct coating thickness measurement of individual tablets during coating process in *real-time* has also been demonstrated. Terahertz technology has the advantages of being non-ionizing, non-destructive, and able to image at depth. In our view terahertz spectroscopy and imaging have significant potential to become industry standards for future pharmaceutical endeavors.

To live up to its enormous inherent potential, terahertz technology has to become fast and affordable, which requires new approaches to many details of the terahertz system architecture. In addition, it would be desirable to extend the spectral range of the current instruments from 100 cm^{-1} to, for example, 300 cm^{-1}. This will allow terahertz spectrum to cover both the inter-molecular and some of the intra-molecular vibration modes of pharmaceuticals, thus providing better spectral specificity for chemical discrimination and mapping. The broader spectral coverage would also help to characterize thinner coating layer with higher spatial resolution. Quantum chemical modeling is another area of interest, and advances in computational simulation of terahertz spectra would help to fully interpret/understand the vibration modes of pharmaceutical solids. These technological advances will be of significant importance in improving the ultimate understanding of pharmaceutical materials, formulations and processes.

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