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Terahertz pulsed spectroscopy and imaging in the pharmaceutical setting – a review

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Abstract

Terahertz pulsed spectroscopy (TPS) and terahertz pulsed imaging (TPI) are two novel techniques for the physical characterization of pharmaceutical drug materials and final solid dosage forms, utilizing spectral information in the far infrared region of the electromagnetic spectrum. This review focuses on the development and performance of pharmaceutical applications of terahertz technology compared with other tools for physical characterization. TPS can be used to characterize crystalline properties of drugs and excipients. Different polymorphic forms of a drug can be readily distinguished and quantified. Recent developments towards a better understanding of the fundamental theory behind spectroscopy in the far infrared have been discussed. Applications for TPI include the measurement of coating thickness and uniformity in coated pharmaceutical tablets, structural imaging and 3D chemical imaging of solid dosage forms.

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Terahertz technology

Over the past few years terahertz technology has become a new tool for the physical characterization of solid materials (Beard et al 2002). Radiation in the far-infrared region of the electromagnetic spectrum, so-called terahertz radiation (60 GHz–4 THz = 2–130 cm^{-1}, Figure 1), is used to study pharmaceutical materials. Both imaging and spectroscopic measurements have been developed. Using this technology it is possible to directly access and exploit structural information of condensed matter at unparalleled speed. The energies of terahertz radiation are lower than most internal vibrations of the molecules and the predominant mode of absorption of terahertz radiation is due to intermolecular vibrations. Rather than probing intramolecular vibrations, terahertz spectra represent information on translations and liberations of molecules (Chantry 1971). It is an excellent technique for characterizing the crystalline properties of solid materials, as the phonon lattice modes are probed directly.

Traditionally, radiation in the part of the electromagnetic spectrum in question has been generated by sources of incoherent blackbody radiation such as mercury arc lamps (Chantry 1971). Extremely sensitive cryogen cooled heat detectors, so called bolometers, were necessary to detect the signals. Due to the difficulties arising from the combination of weak sources of radiation and the elaborate detection process, only few specialist groups have been studying materials properties in this spectral range.

Using femtosecond lasers and specially-designed photoconductive semiconductor antenna switches, terahertz radiation can be generated and detected at room temperature using a time-gated coherent detection scheme (Taday & Newnham 2004) (Figure 2). Pulses of laser light, with photon energy greater than the bandgap of the gallium arsenide (GaAs) semiconductor, generate electron-hole pairs in the substrate. These photo-injected charge-carriers are subsequently accelerated through the substrate by a direct current electric field. The devices are manufactured as antennae producing short bursts of coherent broadband radiation in the far-infrared with each pulse of laser light (Auston 1975; Leitenstorfer et al 2000) (Figure 3). The coherent nature of the radiation and the detection scheme used allow the direct measurement of the terahertz electric field. Therefore, not only the spectral absorption coefficients can be determined but also the spectral refractive indices of the sample can be measured directly.

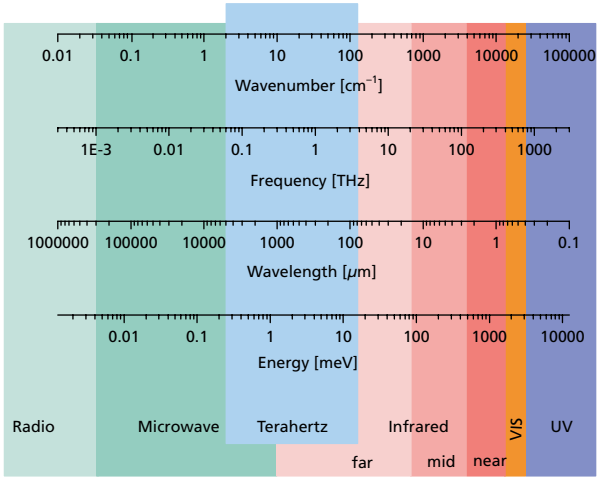

Figure 1 The electromagnetic spectrum showing terahertz radiation in relation to adjacent spectral regimes.

The current generation of instruments can access the spectral range 2–130 cm^{-1} (Taday & Newnham 2004). Little or no maintenance is required to operate these instruments. The instruments are quite compact and portable as there is no need for sophisticated cooling solutions. Recording a high quality terahertz spectrum with a spectral resolution of 1 cm^{-1} can be achieved in well under one minute. Terahertz pulsed spectroscopy (TPS) is a fast and non-destructive technique. For time-critical applications a spectrum can be acquired in a couple of milliseconds, making it a potential tool for in-line processes monitoring. The power of the terahertz radiation is far less than 1 μW and, as this level of radiation is below the thermal background, thermal strain induced in the sample is negligible. Standard sampling techniques used for vibrational spectroscopy such as transmission, specular reflection, diffuse reflection and attenuated total reflection (ATR) can be used.

A detailed description of the different methods to generate and detect terahertz radiation would go far beyond the call of this article. Very good and detailed technical reviews on this topic were recently published by Beard et al (2002) and Schmuttenmaer (2004). Wallace et al (2004a) give a brief introduction into early applications of terahertz technology in the pharmaceutical sciences.

Terahertz pulsed spectroscopy

Sample preparation

In TPS, as in FTIR, the sample material has to be mixed with a diluent and then compressed into a pellet before the acquisition of the transmission spectrum. Polyethylene and poly(tetrafluorethylene) (PTFE) are transparent to terahertz radiation and are therefore typically used as diluent materials. Depending on the absorption coefficient of the sample, between 5–40 mg of the sample is dispersed in polyethylene or PTFE powder. It is then compressed into a pellet with a thickness of approximately 0.5–3 mm and a diameter between 5 and 30 mm. The particle size of both sample and diluent is preferably below 100 μm to minimize scattering. Pellets with a thickness of approximately 3 mm have the advantage of preventing the acquisition of multiple reflections of the terahertz pulse, which would lead to etaloning artefacts in the recorded spectra.

Alternatively, if the sample material compacts well, sample pellets can be prepared by direct compression without any diluent. The terahertz radiation provided by modern pulsed sources is usually strong enough to penetrate through thin, undiluted pellets of most pharmaceutical materials.

Among other gases, atmospheric water vapour exhibits a very strong rotational spectrum in the terahertz range. Compared

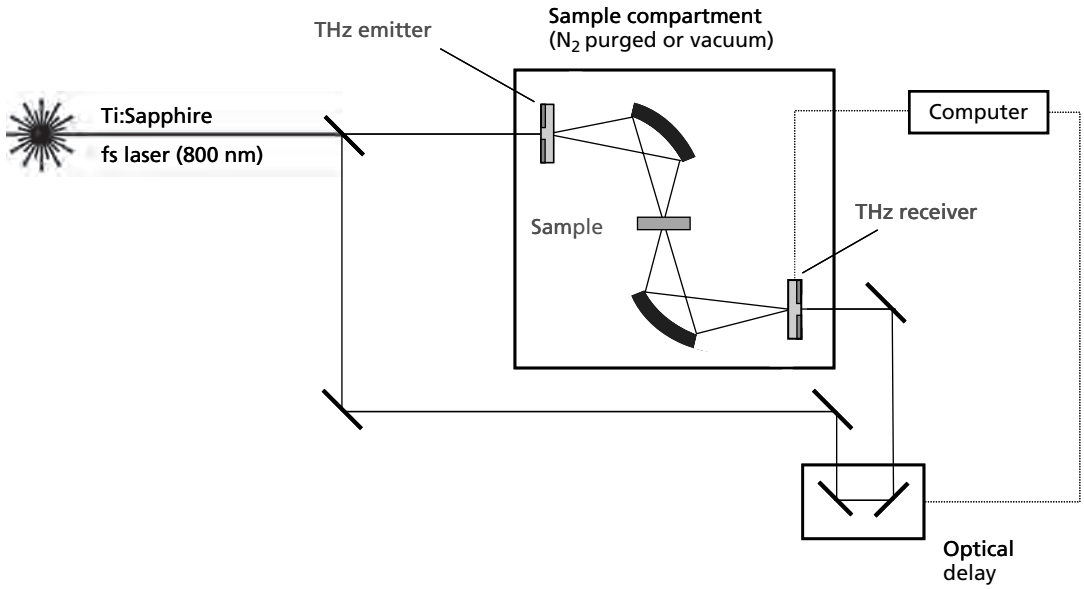

Figure 2 Schematic of a typical terahertz pulsed spectroscopy configuration.

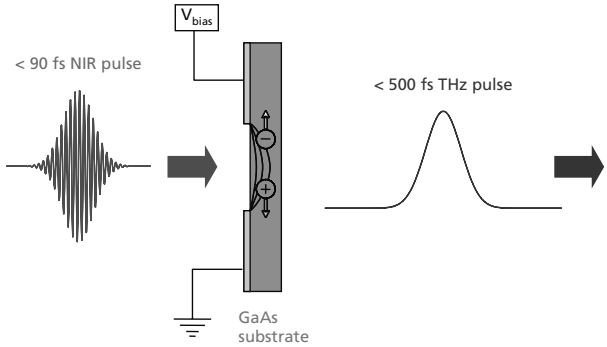

Figure 3 Generation of pulsed terahertz radiation in a gallium arsenide (GaAs) optical switch.

with the terahertz spectra of solids, the peaks observed in the rotational spectra are, in general, more intense and very narrow. Consequently, they can be easily distinguished from spectral signatures of solid materials. To minimize the contribution of the water vapour to the sample spectrum, the sample chamber is either purged with dry nitrogen or evacuated throughout the measurements.

Recently, ATR has become available as an alternative sampling technique for terahertz spectroscopy. In ATR the sample material is placed directly onto a crystal with a very high refractive index. For terahertz ATR spectroscopy, silicon is most widely used for this crystal. By irradiating the terahertz light at an angle greater than the critical angle into the crystal from below, total internal reflection is observed at the interface between the high refractive index crystal and the sample material on top. However, part of the terahertz electric field, the so-called evanescent wave, interacts with the sample material. Using ATR, terahertz spectra of sample powders or liquids placed in good optical contact with the silicon crystal can be acquired within seconds. No sample preparation is necessary.

Comparison of terahertz pulsed spectroscopy to other tools in physical characterization

Compared with other spectroscopic techniques, terahertz spectroscopy has a number of advantages for the physical characterization of pharmaceutical solids in general and polymorphic forms in particular. Polymorphism is a well known phenomenon for many organic molecular crystals, where the same compound can crystallize in a number of different crystal structures (Threlfall 1995; Brittain 1999; Bernstein 2002). This is more prevalent in complex molecules and, even though one crystal structure will be thermodynamically favoured because it has the lowest lattice energy, polymorphic forms can still be very stable, as the energy barriers for the transition from one form to the other can be relatively high (Burger & Ramberger 1979a, b). In mid- and near-infrared spectroscopy the information provided only gives indirect information about crystalline structure. The spectra, representing intramolecular vibrations, change very subtly with the molecules arranging themselves in different crystal structures. Only in very strong hydrogen-bonded networks do different polymorphic structures lead to pronounced differences in their infrared spectra. The spectra contain much chemical, but limited structural, information. In contrast, terahertz spectroscopy probes lattice phonon modes, which have their origin directly in the crystal structure. Terahertz spectroscopy combines speed, the ease of sample preparation and the broad range of possible accessories and sampling techniques readily available in vibrational spectroscopy. It also provides sensitivity to periodic structural changes within the sample comparable with X-ray powder diffraction (XRPD). Complementary information about lattice modes could also be recorded by low-frequency Raman spectroscopy. However, acquiring these spectra is much more difficult and time-consuming than using TPS. Raman measurements involve well-aligned triple-grating Raman spectrometers, long acquisition times, comparatively high power laser excitation, and possible difficulties caused by resonance effects and fluorescence. Low wavenumber Raman spectra cannot be recorded on standard FT Raman instruments due to the difficulty separating Rayleigh scattering from Stokes scattering at shifts close to the excitation wavelength. An additional problem with Raman spectroscopy is the high laser excitation power necessary to generate a signal, which can lead to thermal strain in the sample (Johansson et al 2002). Polymorphic transitions induced by localized heating of the sample are possible.

TPS in ATR mode is an interesting tool for polymorph screening, as only milligrams of sample material are necessary for analysis. In contrast to XRPD no preferred orientation effects are observed in terahertz spectroscopy. Even though the terahertz spectra cannot provide the same amount of information as XRPD, such as the unit cell dimensions, they are still extremely sensitive to the crystalline form of the material. Analysis of the crystal form by terahertz spectroscopy is much quicker than XRPD, induces less strain on the sample and is less affected by measurement artefacts such as preferred orientation. None or only minimal sample preparation is required and a tablet can be used directly, whereas XRPD usually requires sample preparation and a powder sample. Even though terahertz spectroscopy will not be able to replace a thorough crystal structure determination, it is a valuable tool for screening materials and identifying polymorphic forms quickly without complex procedures and inherent time delays.

Solid-state nuclear magnetic resonance (ssNMR) is another very powerful and well-established tool for the characterization of pharmaceutical solids. It has been widely used to investigate properties of polymorphic forms and has been proved to be a very accurate and versatile technique (Bugay 1993; Apperley et al 1999). It is not affected by preferred orientation effects. However, long range information in ssNMR spectra is somewhat limited due to the fact that measurements are based on the local environment rather than periodic structures (Threlfall 1995). In this respect the information obtained is as indirect as mid-infrared spectroscopy, but ssNMR spectra still show differences in polymorphic forms very reliably, due to the high sensitivity and accuracy of the measurements. A problem with ssNMR is that it requires a large amount of sample material, and that sample needs to be spun at very high speed at a certain angle to the magnetic field throughout the measurement to achieve an appropriate

resolution (magic angle spinning). The acquisition time for a single spectrum with a decent signal-to-noise ratio is still well above one hour, which is a major shortcoming of this technology at present. Moreover, the equipment is large, immobile and bulky, with heavy magnets and special requirements for cooling, maintenance and installation.

Terahertz spectroscopy addresses the inter-molecular structure and tends to contain physical information rather than chemical, as can be observed by ssNMR and IR. TPS instruments currently cover the wave range between 2–133 cm^{-1}, but very recently terahertz devices have been developed which emit at frequencies up to 180 cm^{-1}. This information leads to spectra that are very sensitive to structural properties of the sample. Even though it could be shown that, for a rigid dimer molecular structure such as carbamazepine, the phonon modes are restricted to the wavenumber range between 10–140 cm^{-1} (Day et al 2006), this might not be true for more flexible polymorphic forms. In all the different polymorphic substances investigated so far it was possible to distinguish the different forms from one another. Little chemical specificity can be achieved with information in this spectral range due to the lack of intramolecular modes. Most intramolecular vibrations are expected at wavenumbers above 200 cm^{-1}. Hence it would be desirable to extend the spectral bandwidth of the instruments to include measurement of at least some of the intramolecular vibrations.

A number of pharmaceutical excipients are amorphous and therefore do not show any spectral contribution other than diffuse absorption to the terahertz spectra at the present stage. It is possible that the short range order in the amorphous state between neighbouring molecules contribute to the terahertz spectra at higher wavenumbers. Thus an extended bandwidth could make terahertz spectroscopy an extremely valuable tool to characterize amorphous materials. In terms of the characterization of the crystalline properties of APIs, the lack of spectral signatures at low wavenumbers is an advantage as it allows clear observation of crystalline properties.

Crystallinity – qualitative characterization

In the pharmaceutical industry the characterization and control of all possible polymorphic forms of a new active pharmaceutical ingredient (API) are key factors for successful product development, patent protection and life cycle management (Dunitz & Bernstein 1995; Henck et al 2001; Grant & Byrn 2004; Bernstein 2005). Solid-state conversion processes between the different forms are common (Bernstein 2002). It is important to understand these processes in the early development stage of a formulation to control the stability of the API and chose the optimal polymorphic form for the product. Almost all new chemical entities (NCE) are known to exhibit polymorphic forms, as are many of the drugs on the market (McCrone 1965; Bernstein 2005).

With the advent of high-throughput screening, more and more NCE are showing solubility problems and are classified as class II drugs according to the Biopharmaceutics Classification System (BCS, class II: low solubility, high permeability). Frequently, these NCE have a large molecular weight and lipophilic properties (Wu & Benet 2005). From the formulation perspective there are a number of different approaches to enhance the solubility of the API, such as formulation of the active as a solid solution, solid dispersion or in the amorphous state within a crystalline matrix (Leuner & Dressman 2000; Yu 2001). Independent of the approach chosen to enhance the solubility of a BCS class II drug, it is crucial to be able to monitor the crystallinity of a sample and to understand its conversion processes from the amorphous state back to the crystalline state.

Despite the fact that TPS has only recently become available commercially, a number of studies have investigated the potential of terahertz spectroscopy for the characterization of pharmaceutical solids. Walther et al (2000) showed absorbance spectra and refractive index data for different retinal samples, and the monosaccharides glucose and fructose, as well as the disaccharide sucrose (Walther et al 2003). For the sugars, both crystalline and amorphous samples were measured at room temperature and 10 K. In the amorphous state only diffuse absorption, increasing with wavenumber, could be observed (Figure 4) (Walther et al 2003). This type of behaviour was observed also for amorphous indometacin (Strachan et al 2004). Walther et al (2003) and Strachan et al (2004) both attributed this to a lack of intermolecular long range order in the amorphous sample compared with the hydrogen-bonded polycrystalline material.

In an initial study by Taday et al (2003b), the ability to distinguish between two different polymorphic forms of ranitidine hydrochloride using TPS was demonstrated. Not only was it possible to detect differences between pure specimens of the polymorphs but, equally, the transmission

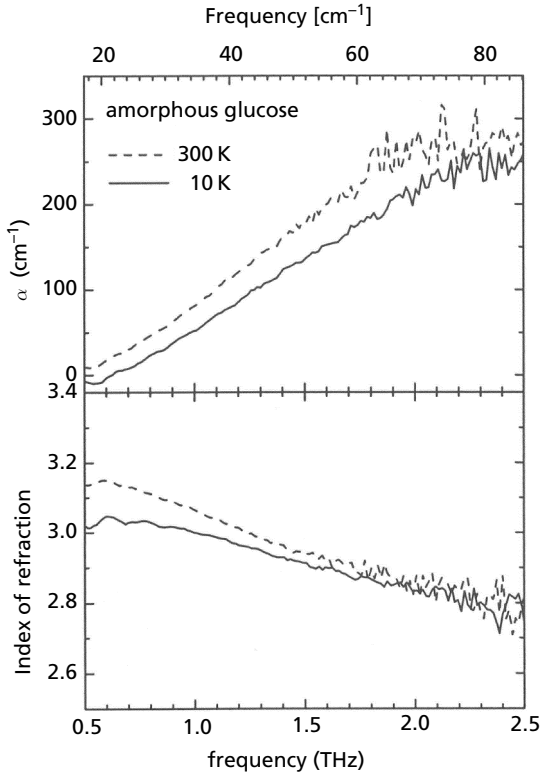

Figure 4 Terahertz pulsed spectra of amorphous glucose showing (top) the absorption coefficients and (bottom) refractive indices (reprinted from Walther et al (2003) with permission from Elsevier).

spectra of formulated commercial tablets allowed the specific polymorphic forms in the tablet formulation to be distinguished. This work was the first direct application of terahertz spectroscopy to the pharmaceutical sciences with an emphasis on demonstrating the potential of this technique for pharmaceutical solid-state characterization. The analysis was of a qualitative nature and no figures of merit were reported.

Further work into the characterization of crystalline properties of different drugs has been carried out on four model compounds (Strachan et al 2004). Spectra of the carbamazepine polymorphic forms I and III (Figure 5A), as well as enalapril maleate I and II (Figure 5B), were reported. In all cases the terahertz spectra showed distinct differences between the polymorphs as well as between different crystalline states. The authors demonstrated that, by using TPS, it was possible to readily distinguish the amorphous from the crystalline state in indometacin (Figure 5C) and also between crystalline and liquid crystalline fenoprofen calcium (Figure 5D) (Strachan et al 2004). As the lattice order in these systems decreases the phonon modes become weaker. With insufficient long range order the phonon modes can no longer be sustained. In the amorphous state the terahertz spectrum exhibits diffuse absorption and no sharp spectral features can be observed.

Sulfathiazole, a drug with five known polymorphic forms, has been investigated using TPS (Zeitler et al 2006c). It was found that TPS possessed some advantages over other techniques. Sulfathiazole is a classic polymorphic system, with studies extending well over sixty years (Burger & Dialer 1983). Despite the extensive research on the polymorphism of sulfathiazole over the years, a new polymorph was identified recently (Hughes et al 1999). Using TPS, all known polymorphs of sulfathiazole were readily distinguished by their terahertz spectra (Figure 6). In this particular complex polymorphic system, a number of effects complicate polymorph identification by XRPD or mid-IR spectroscopy (Apperley et al 1999). It is necessary to use more than one of these techniques to confidently identify the polymorphic form. Using a terahertz ATR accessory, the identification of all five polymorphic forms of sulfathiazole takes only seconds by TPS with no sample preparation. 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-infrared (Zeitler et al 2006c).

Not only can different polymorphic forms of drugs be distinguished by their terahertz spectra, but it is possible to differentiate between different hydrate forms. Lactose, one

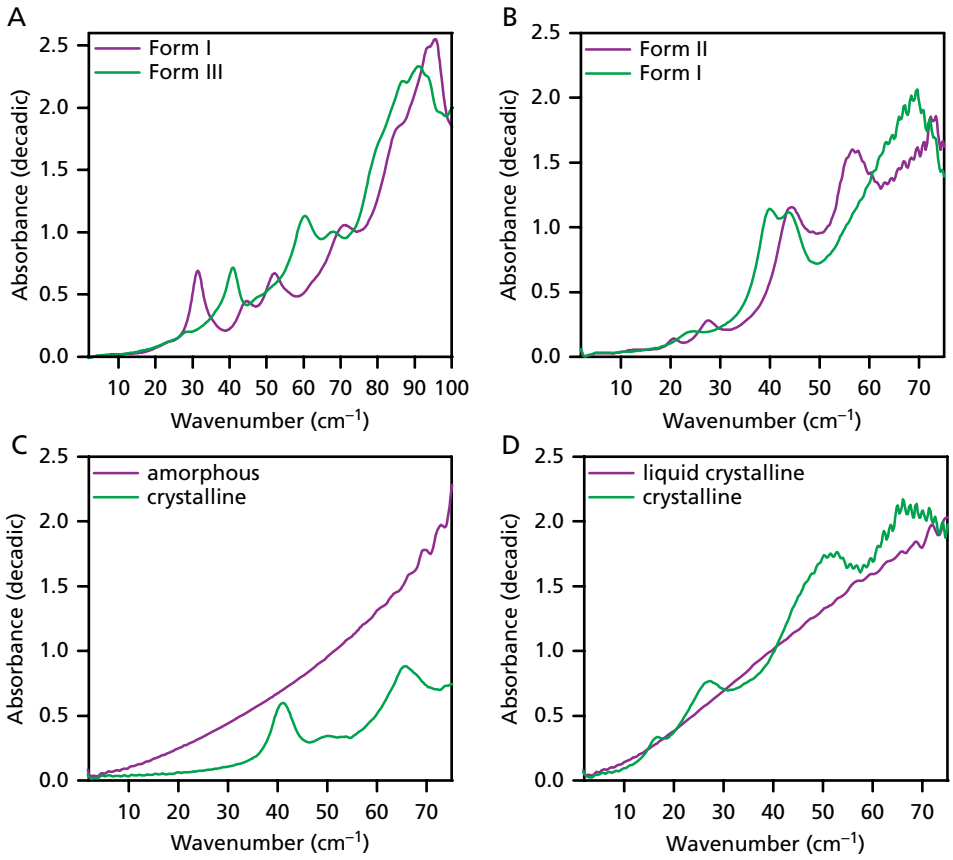

Figure 5 Terahertz spectra of different pharmaceutical drugs. A. Carbamazepine polymorphs I and III. B. Enalapril maleate forms I and II. C. Crystalline and amorphous indometacin. D. Liquid crystalline and crystalline fenoprofen calcium (reprinted with modifications from Strachan et al (2004) with permission from Elsevier).

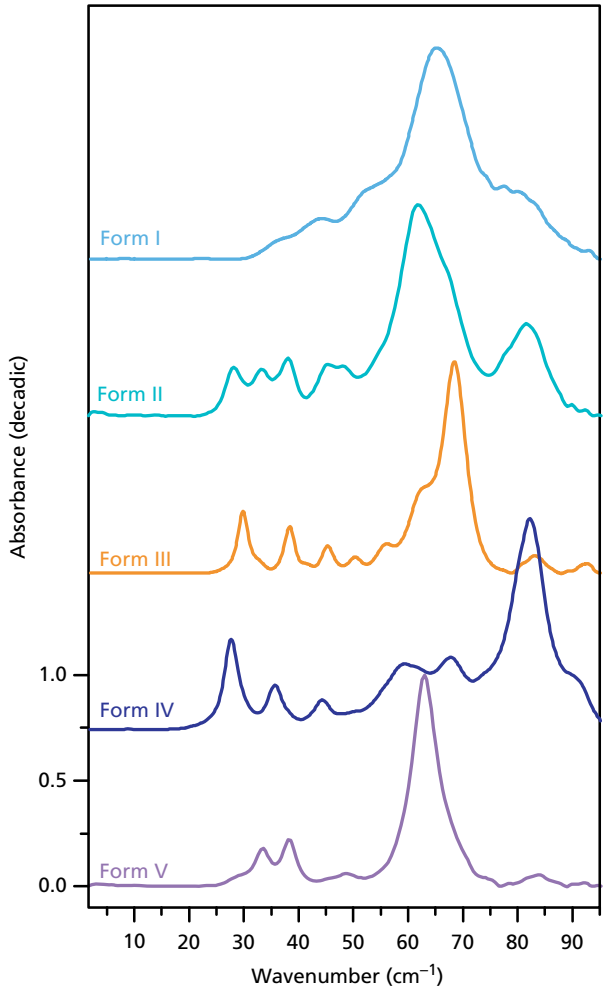

Figure 6 Terahertz spectra of the five polymorphic forms of sulfathiazole. Spectra are vertically offset, background corrected, and normalized for clarity (reprinted with modifications from Zeitler et al (2006c) with permission from Wiley).

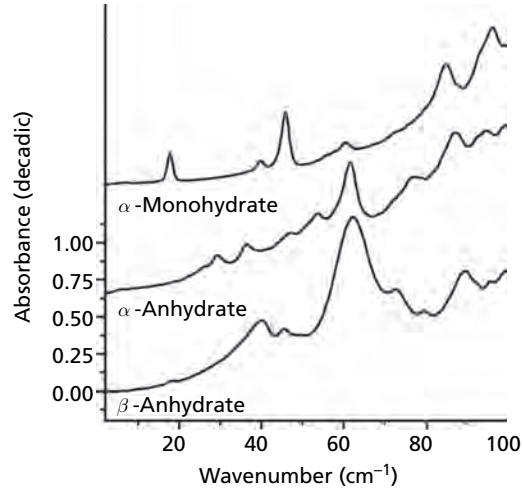

Figure 7 Terahertz spectra of three commonly-used hydrate forms of lactose. Spectra are vertically offset and normalized for clarity.

of the most commonly used excipients in the pharmaceutical industry, forms at least three different hydrates. The most widely used are lactose α-monohydrate, the α-anhydrate, and a β-anhydrate form. These three hydrate forms exhibit terahertz spectra with distinct features (Figure 7) (Zeitler et al 2006b). Theophylline monohydrate and its anhydrous forms can be readily discriminated by TPS (Upadhya et al 2006).

Examples of other crystalline pharmaceutical materials that have been reported in the literature using TPS include acetylsalicylic acid, benzoic acid (Walther et al 2002), D-glucose (Upadhya et al 2003), D-mannose, D-galactose, D-fructose, D-maltose, β-lactose (Upadhya et al 2004), cocaine, morphine, lactose α-monohydrate (Fischer et al 2005a), and methamphetamine (Ning et al 2005).

Crystallinity – quantification

The applicability of terahertz spectroscopy for quantitative analysis has been investigated. The amount of acetylsalicylic acid and paracetamol was quantified in the presence of the excipients lactose and cellulose in a proof-of-principle study (Taday 2004). The spectral features of the active ingredients and both excipients did not overlap, allowing the quantitative determination of the API in the presence of the excipients without any further sample preparation. The data analysis was performed using a chemometric model based on the partial least squares (PLS) algorithm.

Furthermore, the ability of TPS to quantify polymorphic forms in binary mixtures was studied (Strachan et al 2005). Again, different forms of carbamazepine, enalapril maleate, indometacin, and fenoprofen calcium were selected as model systems. Binary powder mixtures of 0–10% and 0–100% of one crystalline form in the other of the same drug were measured (Figure 8A). Multivariate analysis (PLS) was performed. Limits of detection of one crystalline form in the other as low as 1.5% were reported (Figure 8B). The limits of detection were determined according to the ICH guidelines (ICH 1996). This study demonstrated that, by using TPS, it was possible to obtain quantitative information that was comparable with, or better than, that using other physical characterization tools (Bugay et al 1996; Mackin et al 2002; Pratiwi et al 2002; Saunders et al 2004; Byard et al 2005). However, limits of detection are often more dependent on the sample material rather than the analytical technique itself and the performance of certain techniques should only be compared with the same compound. So far no detailed study has been published on the validation of a polymorphic quantification by TPS i.e. in a dosage form.

Phase transitions in solids

Terahertz spectroscopy has been used to study the mechanisms and dynamics of a polymorphic conversion process (Zeitler et al 2005b). For these experiments a variable temperature cell was used. Typically, the heating rate was between 1 and 10 K min^{-1}. The transformation of carbamazepine form III to form I was monitored by temperature-dependent terahertz measurements. Two transformation processes, one via a melt and the other one via a solid-state reaction, were distinguished from one another by temperature-dependent

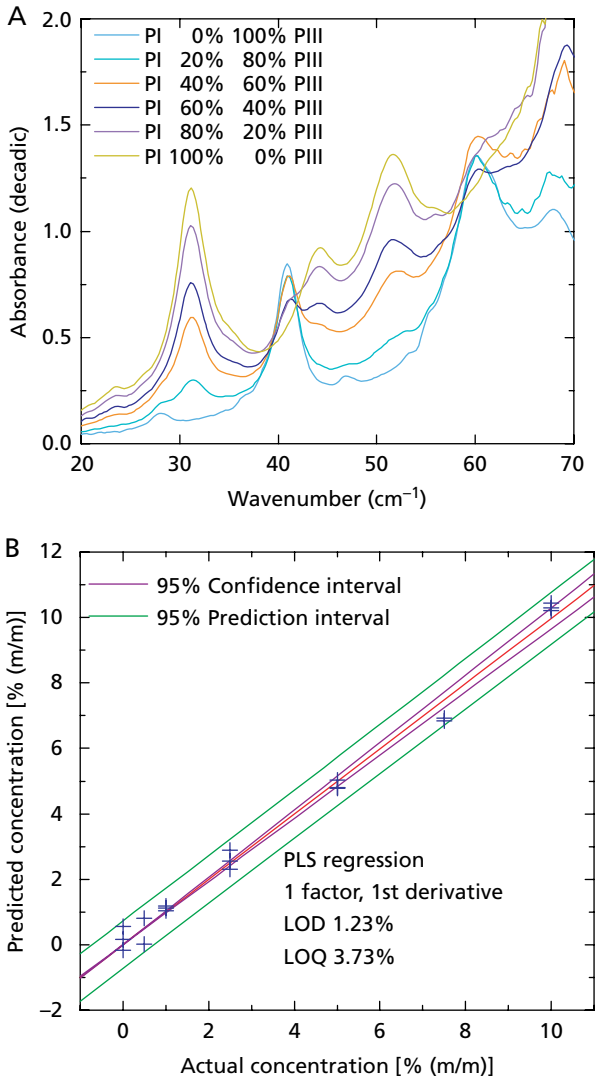

Figure 8 Quantification of carbamazepine polymorphs. A. Physical mixtures of carbamazepine form III and I. B. Calibration of the predicted concentration of carbamazepine form III in its physical mixture with form I (reprinted with modifications from Strachan et al (2005) with permission from Wiley).

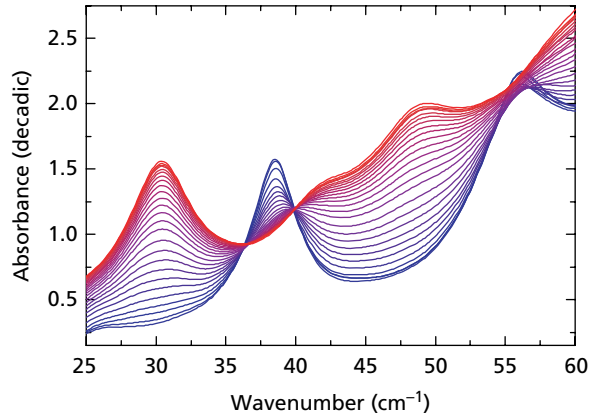

Figure 9 The solid-solid conversion of carbamazepine form III (blue) to I (red) at isothermal conditions (433 K). Spectra were recorded at 5-min intervals until the transformation was complete (reprinted with modifications from Zeitler et al (2005b) with permission from Elsevier).

terahertz spectroscopy. The solid-state transformation process (Figure 9) was studied in detail.

For the different polymorphic forms of sulfathiazole, the phase transitions between the five polymorphs were characterized and compared with data from thermal analysis (Zeitler et al 2006c). The polymorphic purity of the sample material was analysed by temperature-dependent TPS measurements. The additional advantages of terahertz spectroscopy were apparent. TPS can be used to study very fast solid-state processes without influencing the experimental conditions. Good quality spectra can be acquired in much less then a second. As the terahertz power is orders of magnitude lower than other techniques, such as Raman spectroscopy, no sample heating effects are observed (Johansson et al 2002). This makes terahertz spectroscopy particularly suitable for the analysis of temperature-sensitive samples and phase transitions.

Terahertz spectroscopy can provide complementary data to help interpret thermal analysis data, such as differential scanning calorimetry and thermogravimetric analysis. It adds structural information to the thermodynamic information obtained by thermal analysis.

The ability to study phase transitions between polymorphic forms is not restricted to pure specimens but can also be performed on formulated products. As a model system a tablet containing carbamazepine, α-lactose monohydrate, magnesium stearate, and talc was used to study the conversion process in transmission (Zeitler et al 2005a). Upon heating the tablets, the dehydration of lactose followed by the polymorphic transition of carbamazepine form III to form I, could be monitored in-situ without any further sample preparation.

Terahertz spectroscopy in the life sciences

A number of groups have investigated the potential of TPS to study materials and samples in the life sciences. Terahertz spectra of DNA, bovine serum albumin, collagen (Markelz et al 2000), the nucleic acids and nucleosides (Fischer et al 2002), purine and adenine (Shen et al 2003), short-chain polypeptides (Kutteruf et al 2003), oligopeptides and amino acids (Korter et al 2003), L-glutamic acid (Taday et al 2003a), artificial RNA (Fischer et al 2005b), a single-strand oligonucleotide sequence (Fischer et al 2005a), α- and γ-glycine (Shi & Wang 2005), serine and glycine (Korter et al 2006), and cytosine (Shen et al 2005a) have been reported. Again, a detailed discussion of these findings would go beyond the scope of this review.

Interpretation of terahertz absorption spectra of crystalline materials

The fact that the spectral features in this region of the electromagnetic spectrum are dominated by intermolecular interactions, rather than intramolecular vibrations, makes terahertz spectroscopy a unique tool for the physical characterization of pharmaceutical solids. However, the understanding of

terahertz spectra is still in its infancy and further work is necessary to find out more about the nature of the spectral features and the underlying structural information.

Chen at al (2004) have published an initial attempt to assign modes in the terahertz region by using density functional theory (DFT) to model vibrations of single molecules in the gas phase. Using a similar approach Zeitler et al (2005b) presented calculations of low frequency vibrations of carbamazepine. Carbamazepine forms strong amide–amide hydrogen bonded dimers in all its solid polymorphic modifications. Single molecule DFT calculations were compared with calculations of the hydrogen bonded dimer structure. As terahertz spectra of the different polymorphic modifications of carbamazepine are very different it is not surprising that such a simplified computational model does not produce accurate predictions. Nonetheless, some insight into possible intramolecular vibrations can be gained. For the molecule of the DNA base thymine, Fischer et al (2005a) calculated low frequency spectra also by using DFT. They calculated the terahertz spectra for the single molecule and clusters of up to eight molecules. For the comparatively simple crystal structure, the authors found a relatively good agreement between the calculations and their experimental spectra at 10 K. However, they stress the point that for most molecular crystals this might not be the case, as the crystalline structure in this particular example is very simple compared with the majority of organic molecular crystals. Ning et al (2005) attempted to explain their experimental spectra of methamphetamine again using the approach of isolated single molecule gas phase measurements. They presented a calculation of intramolecular vibrations that compared quite well to the experimental spectrum, even though the experiment was conducted at room temperature and the calculations did not incorporate any theory of solid-state properties. Hydrogen bonding is absent in methamphetamine, so no mixing with the lattice modes occurred. Again, the crystal structure of methamphetamine is quite simple.

In another study, Day et al (2006) correlated spectra of two different carbamazepine polymorphic forms measured at 7 K with rigid molecule atomistic lattice dynamics calculations based on energy minimized crystal structures. In this more complex model, the solid-state properties of the sample were included into the calculations. This allowed the calculation of the low frequency modes for different crystal structures of the same compound. The molecules were treated as rigid bodies in a point mass lattice and only intermolecular vibrations were calculated using only non-empirically derived factors. Different harmonic vibrational modes were calculated for all four known polymorphic forms of carbamazepine. Tentative assignments were made to the observed modes of the experimental spectra (Figure 10) and critically discussed.

Korter et al (2006) used calculations based on the CHARMM (Chemistry at HARvard Molecular Mechanics) code for macromolecular dynamics simulations and DFT ab initio Car-Parrinello molecular dynamics (CPMD) algorithms. They presented calculated terahertz spectra for serine and cysteine and compared them with the experimentally acquired data at 77 K and room temperature. Again, tentative assignments were made.

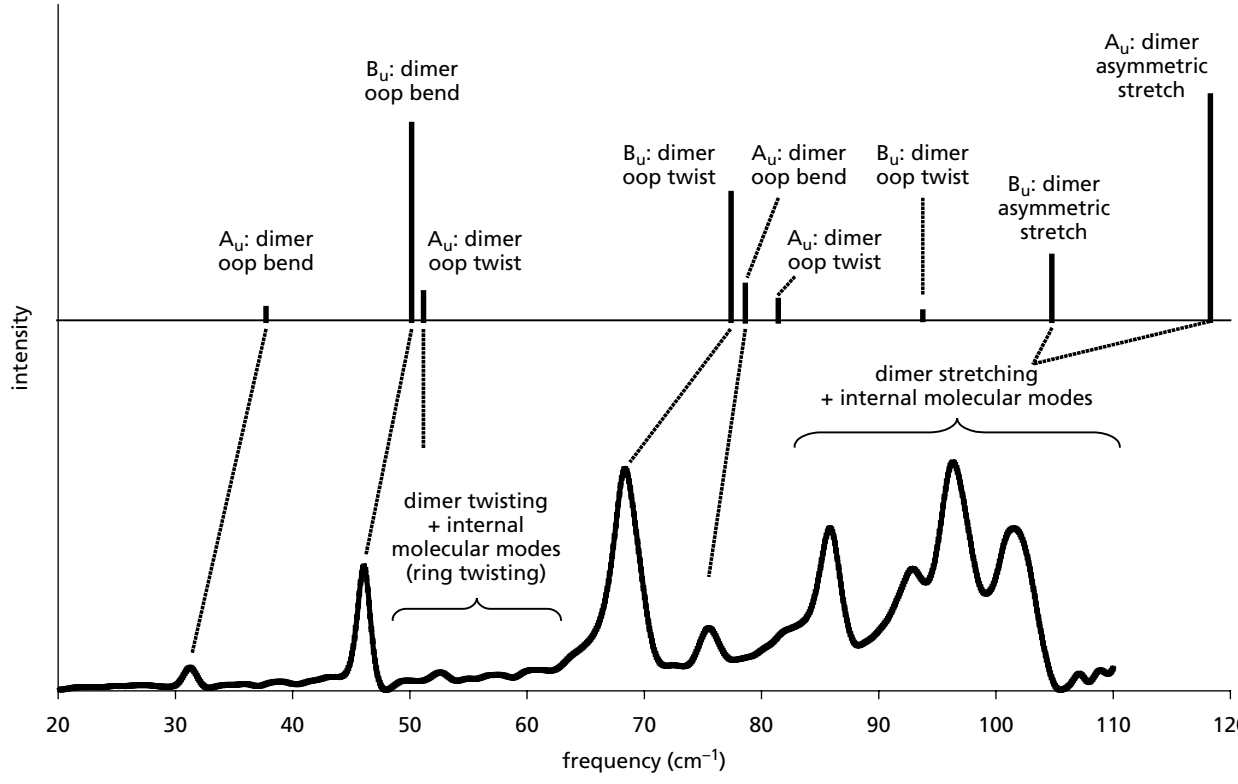

Figure 10 Experimental spectrum of carbamazepine form III 7 K (bottom), calculated harmonic rigid molecule band positions and relative intensities (top), and tentative assignments. The observed spectrum has an empirical baseline function subtracted (oop = out-of-plane) (reprinted with permission from Day et al (2006), Copyright 2006 American Chemical Society).

In a recent work by Allis et al (2006) solid state DFT calculations were presented to calculate terahertz spectra of an explosive material. Periodic boundary conditions were employed to simulate the crystal environment of the sample. This approach has the advantage that anharmonic terms are also incorporated into the calculations. Consequently, the calculations are far more time-consuming. The results of the study indicated that solid-state DFT calculations were a very promising method to calculate low frequency modes with very good agreement between experimental data and calculated data (Figure 11). In addition, the calculations by Allis et al (2006) and Saito et al (2006a, b) give further evidence that the isolated molecule DFT calculations have very limited significance, as all calculated modes for wavenumbers below 120 cm^{-1} using this methodology were shifted to much higher wavenumbers in the solid-state calculations due to crystal packing and intermolecular interactions.

As expected, the studies indicated that the quality of predictions improved with models that accounted for the periodicity of the molecules in the crystalline lattice. Isolated gas phase calculations are useful to augment to the results from the solid-state calculations and to interpret intramolecular vibrations that might start to mix with the phonon modes at higher wavenumbers. However, isolated gas phase calculations should never be used exclusively to explain terahertz spectra without additional calculations taking the solid-state environment into account. The difficulty in calculating terahertz spectra is due to the fact that the algorithms for calculating lattice dynamics are not yet as accessible as the ones for the intramolecular vibrations at higher wavenumbers that are widely available in common software packages. No definitive assignment of the observed experimental modes has been possible; but, using the more advanced solid-state calculations as presented by Day et al (2006), Allis et al (2006) and Saito et al (2006a, b), substantial progress has been made compared with isolated gas phase calculations. No study thus far presents conclusive calculations or an approach that allows experimental terahertz spectra to be readily interpreted. However, this is a very active field of research and work is in progress to gain a better understanding of the low frequency vibrations in crystalline solids.

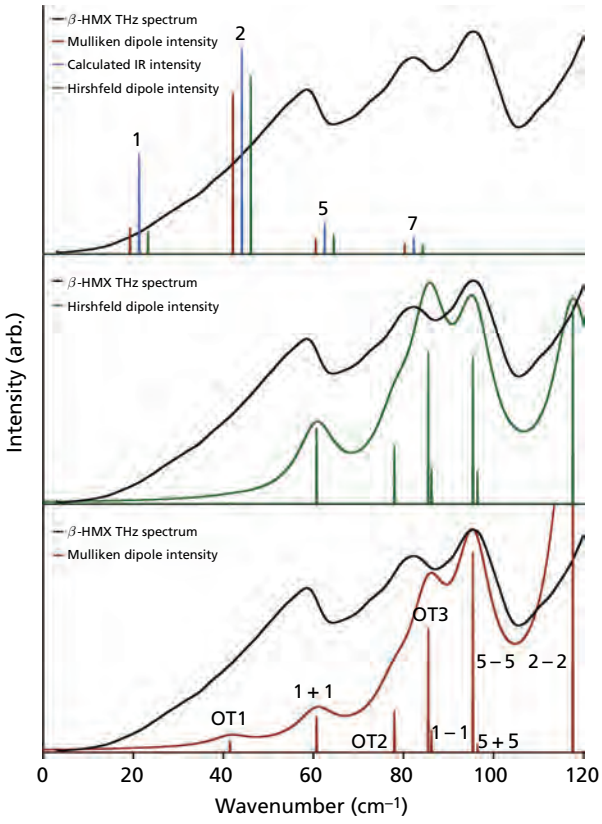

Figure 11 Calculated terahertz spectrum of the explosive β-HMX and comparison with the observed room temperature spectrum (solid black line). The isolated-molecule (top) and solid-state VWN-BP/DNP normal modes (0–120 cm^{-1}) with solid-state intensities provided by the Hirshfeld (middle) and Mulliken (bottom) difference-dipole results. External mode labels are as follows: OT1, optical translation along the AC crystal plane; OT2, optical translation along the AB crystal plane; OT3, optical translation along the BC crystal plane (reprinted with permission from Allis et al (2006), Copyright 2006 American Chemical Society).

Terahertz pulsed imaging

In contrast to imaging with near-infrared (NIR) (Reich 2005), mid-infrared and Raman spectroscopy (Bugay 2001; Chan et al 2003), where the spectral information reflected at each pixel is used to generate a 2D chemical image of the sample surface, terahertz pulsed imaging (TPI) (Figure 12) reveals spatially resolved information from below the surface of the sample. Excipients most commonly used for the formulation of solid dosage forms are transparent, or semi-transparent, to terahertz radiation and hence the pulse of terahertz light can penetrate into the sample matrix. The penetration depth of the terahertz radiation into the sample material is dependent on the material and the power of the terahertz pulse. At present, penetration depths into typical pharmaceutical formulations are between 1 and 3 mm (Zeitler et al 2006a). All information is acquired in a single mapping scan of the surface of the sample. It is not necessary to perform multiple runs to obtain information from different depths within the sample, as is the case for confocal spectroscopic techniques. Reflections of the terahertz pulse from interfaces due to changes in refractive indices within the sample matrix enable the reconstruction of the internal sample structure. The time delay of these reflections relative to the surface reflection is used to calculate 3D structural images of the sample. Imaging in transmission is also possible. In NIR, mid-infrared and Raman spectroscopy, information from just below the surface may be contributing to the reflected signal, but it is not possible to completely resolve this information spatially.

With X-ray microtomography an alternative approach has been introduced to characterize structures within pharmaceutical tablets (Sinka et al 2004). Using this technique it is possible to examine density variations within a tablet – the information solely reflecting the physical properties of the sample. To obtain contrast in the X-ray shadow images, and to distinguish between different structures, a significant difference in density of the material is necessary. Due to the very high resolution of the 3D images, X-ray microtomography is

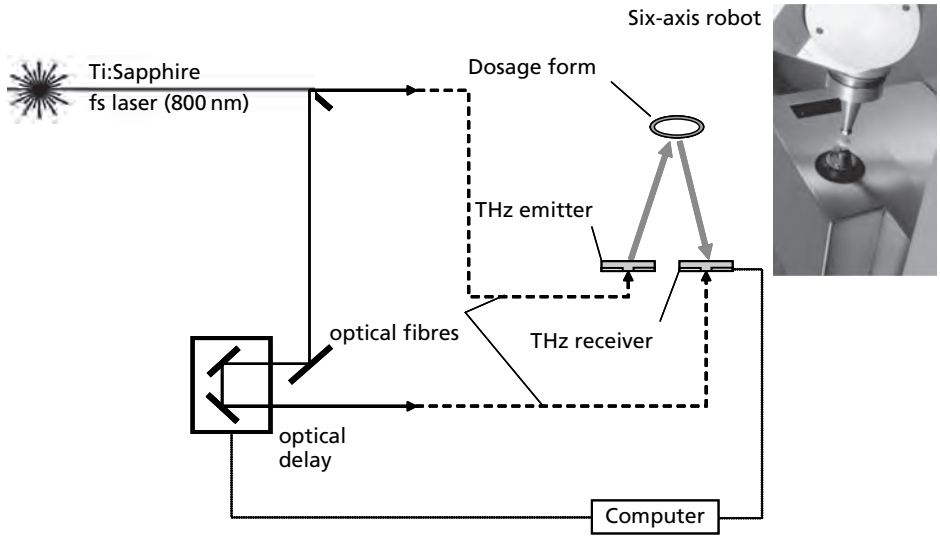

Figure 12 Schematic of a typical terahertz pulsed imaging setup.

potentially very useful in studying properties such as the porosity of a formulation. Long acquisition times, high computational requirements and the possibility of radiation-induced strain in the sample, all limit the applications of this technique. Furthermore, for most tablets it is not possible to acquire high resolution images of the whole sample without cutting the tablet into pieces, as the maximum sample size is limited to approximately 15 mm. To our knowledge there have been no studies on the use of X-ray microtomography in the analysis of coating structures.

Tablet coating analysis

Analysis of tablet coatings is one of the major fields where terahertz technology is being applied to the pharmaceutical sciences. So far, the analysis of coating thickness and integrity has relied predominantly on indirect observations. Coating thickness is typically estimated from the weight gain of the coated tablets compared with the uncoated tablet cores. However, in recent years spectroscopic techniques and imaging approaches have been developed that allow predictions of film coating thickness (Kirsch & Drennen 1995) and film coating processes (Kirsch & Drennen 1996; Romero-Torres et al 2005) based on chemometric models. Even though these techniques revealed much additional information about the quality and integrity of coatings, the images were almost always confined to information reflected from the outside surface of the tablet. A different approach to characterize film coating defects at the interface between tablet coat and core was presented by means of confocal laser scanning microscopy (Ruotsalainen et al 2003). For sugar-coated products no such approach has been developed. To test the coating integrity, it is common practice to perform a dissolution study on part of the production batch. For analysis of the uniformity of a dosage form (Clarke 2004), buried structures within a dosage form, or multiple coating layers, destructive measurements have to be carried out. The tablets have to be cut layer by layer so that spectroscopic images can be acquired from each layer. This process is time-consuming and it is extremely difficult, if not impossible, to analyse such thin structures.

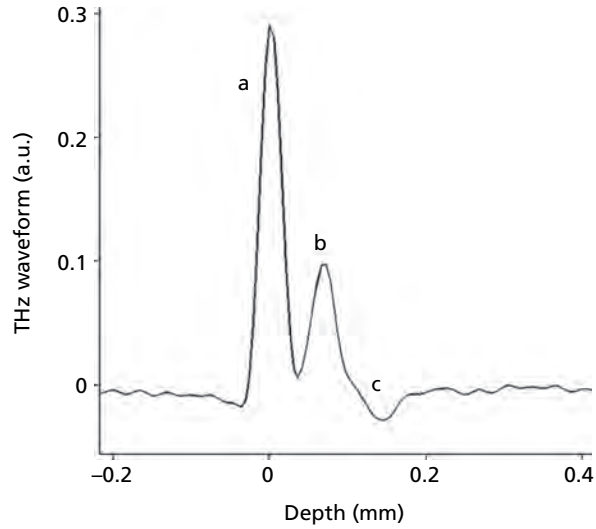

Figure 13 Terahertz (THz) time-domain waveform showing three major features. The positive feature at 0 mm (a) is due to changes in the refractive index between the air atmosphere and the outer coating layer. The second positive peak at approximately 0.1 mm (b) is due to the interface between the outer and inner coating layer. At approximately 0.15 mm a negative peak (c) can be observed representing the interface between the inner coating layer and the core of this bilayered tablet.

As aforementioned, in contrast to the near-infrared and mid-infrared regions of the spectrum, many pharmaceutical excipients used for coating solid-dosage forms are semi-transparent to terahertz radiation. When using pulsed terahertz radiation in reflection, the terahertz pulses can penetrate through the sample and a portion of the signal is reflected back at any interface between materials with different refractive index, such as a new coating layer.

In TPI, terahertz pulses that are reflected back from different coating layers are detected (Figure 13). Each peak in the terahertz waveform corresponds to a different interface

within the sample. With this information the thickness of the coating layers can be determined by measuring the peak-to-peak distance (time delay) of the terahertz pulse. At present a depth resolution of approximately 40 μm can be achieved using this method, with measurement repeatability better than 1 μm. Depending on the tablet size, it takes 10–20 min to acquire the terahertz reflection from the surface of a single side of a tablet with a spectral resolution of 5 cm^{-1} and a spatial resolution of 200 μm (Figure 14).

A fast and non-destructive way to determine the thickness of coating layers on single- or multicoated tablets was proposed by Fitzgerald et al (2005). Those authors discussed the possibility to correlate coating thickness measurements by TPI with its dissolution kinetics, indicating a very promising application of spectroscopic imaging in the process analytical technologies (PAT) framework. So far, no such study has been reported. TPI is sensitive to both the physical and chemical properties of the sample, so terahertz images contain much more information than just the thickness of the coating structure. In sugar-coated tablets it is possible to detect and characterize the fine structure within the relatively thick sugar coat resulting from the discontinuous coating process (Figure 15). It is possible to identify samples where the coating process has been stopped and restarted during the application of a layer. An approach to quantify the quality of the coating, as well as the interface between the coat and the tablet, compares the information of the relative signal strength of the reflection at the coating interface to the reflection from the tablet surface (Shen et al 2005c).

Not only is it possible to quantify the thickness of single or multiple coating layers of a tablet but also the uniformity and integrity of the coat can be analysed (Zeitler et al 2006a) (Figure 14). Problems during a coating process that might lead to a failure of a tablet batch in the dissolution test might be

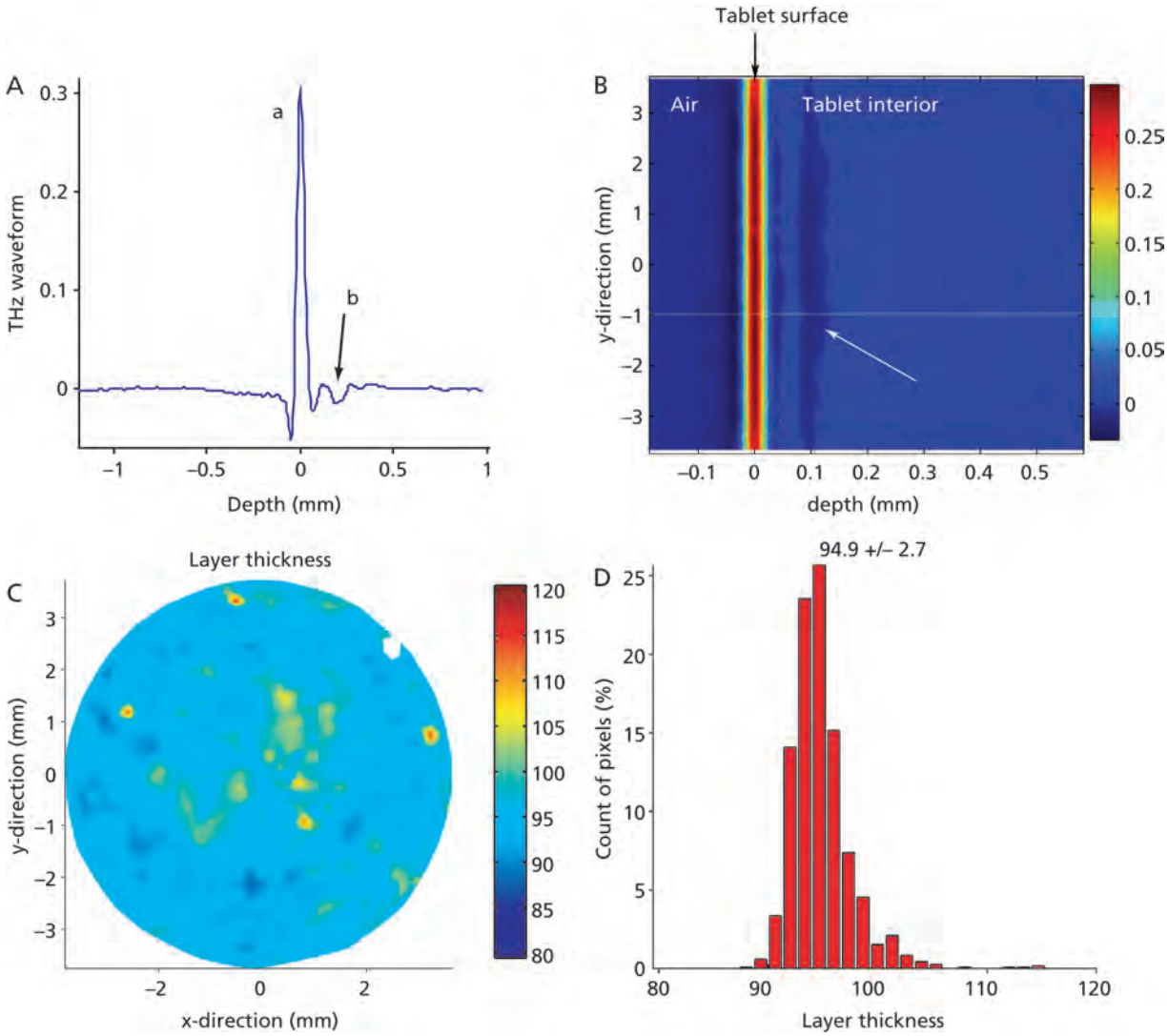

Figure 14 Terahertz pulsed imaging of a film-coated tablet. A. Time domain terahertz (THz) waveform. The dominant peak (a) represents the air-tablet surface interface. The negative peak (b) corresponds to the interface between film coat and tablet core. B. Cross section depth profile of the tablet structure. The arrow indicates the interface between film coat and tablet core. C. False-colour image of the spatial distribution of coating layer thickness. The scale of the colour bar is in μm. D. Histogram for the layer thickness of the outer coating. The scale on the x-axis is in μm.

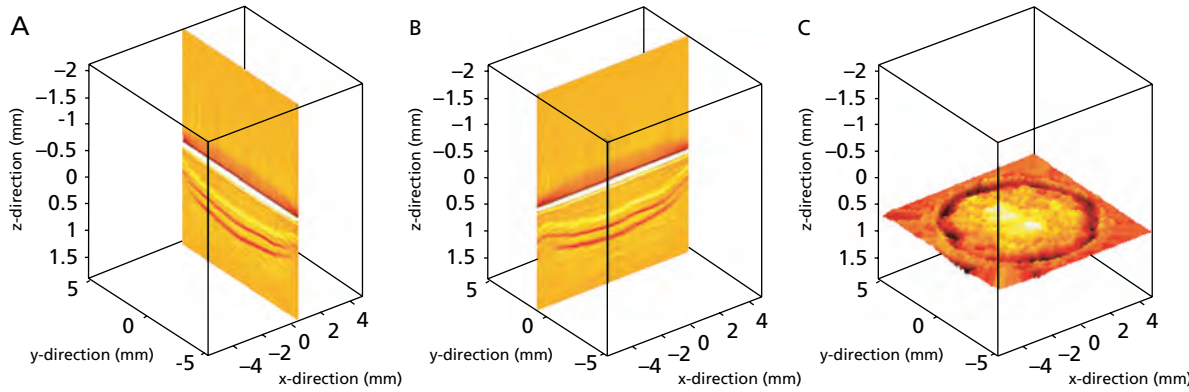

Figure 15 Terahertz pulsed imaging of a sugar-coated tablet. The different interfaces from the polish, colour and sugar layers lead to contrast in the false-colour images. A. Cross section in x-direction. B. Cross section in y-direction. C. Cross section in z-direction.

detectable. As the analysis is non-destructive, the imaged tablets can be used subsequently for the dissolution test, to correlate the terahertz information with their dissolution behaviour.

Non-destructive coating analysis may have an impact on the PAT initiative in the pharmaceutical industry. Currently, the dissolution test of a random sample taken from a production batch determines whether the whole batch passes or fails final inspection at the end of a production cycle. The PAT initiative is trying to change this to an at-line inspection in real time throughout the production cycle, to ensure quality by production leading to improved product safety as well as substantial cost benefits for the manufacturers.

Interfaces and buried structures

Besides the ability to measure the layer thickness of a dosage form, its coating uniformity and spatial coating distribution, TPI can also detect cracks and delamination within a tablet and dislocations of tablet structures. Depending on the absorption of the terahertz pulse by the tablet material, the radiation typically penetrates approximately 3 mm into the sample. This enables the characteristics and quality of the interface between buried structures as in multilayered tablets to be investigated (Zeitler et al 2006a).

Most plastic sheet materials used for pharmaceutical blister packs are transparent to terahertz radiation and their thickness can be readily measured using TPI in reflection. There is no need for the elaborate establishment and validation of chemometric models before the measurements as in NIR (Laasonen et al 2004). A simple transmission measurement of the material is sufficient to determine the terahertz refractive index of the material. It is even possible to characterize the plastic layer of the blister pack sheet and simultaneously analyse the coating of a tablet inside the sealed blister pack.

2D and 3D non-destructive chemical imaging

Combining the technology of TPI for tablet coating analysis and TPS for the analysis of the crystalline properties, and taking them one step further, non-destructive chemical recognition in a three-dimensional object has been performed in a proof-of-principle experiment (Shen et al 2005c). Spectral data were presented for a three-dimensional dataset with two axes describing the horizontal and vertical spatial dimensions, and the z-axis representing the depth information as signal time delay. A four-dimensional dataset was then generated by a time-partitioned Fourier transformation. This allowed the analysis of a pellet containing buried structures of different chemical composition. Different chemicals could be identified by their spectral signature in the 3D matrix of the sample. However promising these first results were, the work has to be considered as the first successful attempt to overcome the multitudinous challenges associated with the data acquisition and processing that need to be mastered to make 3D terahertz spectral imaging routinely applicable.

Further work describes 2D chemical mapping of lactose α-monohydrate, acetylsalicylic acid, sucrose and tartaric acid compressed pellets (Fischer et al 2005a; Shen et al 2005b) (Figure 16).

Terahertz 2D, and especially 3D chemical imaging, would enable the development of a number of exciting applications to further understand and improve pharmaceutical formulations. Layered tablets are increasingly being developed as products to alter the release kinetics of a drug or to combine incompatible drugs or excipients into one system. The recent advances in production technology not only allow these formulations to be produced but also create a demand for new technologies to analyse and understand them.

The development of the 3D terahertz chemical imaging is still in its infancy and needs much further development. This technique potentially has a huge advantage over NIR imaging, as spectral data from within the sample can be acquired without destroying the sample. It would allow the analysis of the distribution of an API within its matrix of excipients before dissolution testing. Another interesting application could be the study of the rate and spatial distribution of drug decomposition processes during stability testing in-situ by quantitative chemometric models.

Outlook

Terahertz technology provides a tremendous opportunity for the pharmaceutical industry: to prevent and detect counterfeit products by providing a non-destructive terahertz ‘structural fingerprint’ of the coating and tablet core structure which is

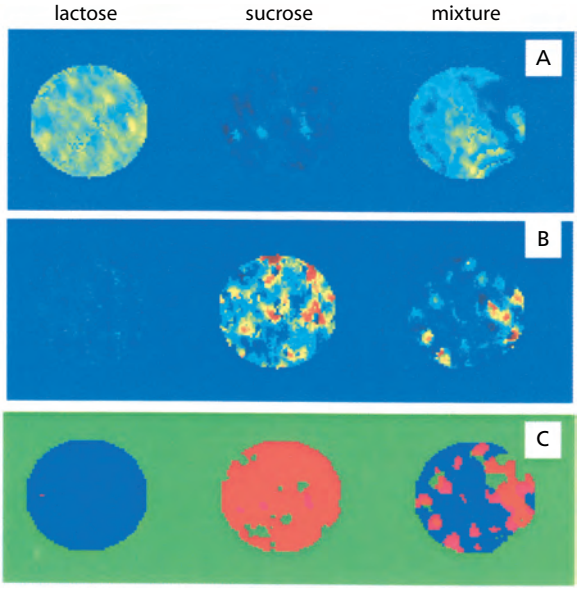

Figure 16 False-colour terahertz chemical mapping image showing the spatial distributions of (A) lactose, (B) sucrose, and (C) reconstructed chemical map of the sample where blue shows lactose, red shows sucrose, pink shows both lactose and sucrose, and green shows neither lactose nor sucrose (reproduced from Shen et al (2005c) with permission from the Institute of Physics).

near impossible for counterfeiters to copy. The rapid drive to develop and apply terahertz technology over recent years has led to a number of promising applications in the pharmaceutical industry. Further potential for this new technology remains to be unveiled and developed. Possible future applications include: enhanced polymorph screening; validation and development of new coating techniques; characterization of innovative new solid controlled-release dosage forms; and resolution of complex bioequivalence issues, to name a few.

This novel technique is in its early days and terahertz technology is still finding its place in the field of physical characterization. The cost associated with the generation of pulsed terahertz radiation by femtosecond lasers is quite substantial at present. A reduction in costs of terahertz systems for specialized applications, such as in-line or at-line monitoring, could be achieved by employing alternative concepts for the generation of terahertz radiation, such as photomixing-based systems of lower-cost diode lasers (Gregory et al 2005) leading to a continuous wave terahertz emission or quantum cascade lasers (Barbieri et al 2004, 2005; Nguyen et al 2006). For the pulsed broadband systems higher power sources and even higher bandwidth would be desirable.

In recent years research in terahertz technology has become dynamic and versatile. With the core technology becoming more mature, the focus has shifted from developing terahertz devices towards application development. This has resulted in numerous applications in materials characterization, ranging from medical imaging (Wallace et al 2004b) and security applications (Shen et al 2005d), to the applications in the pharmaceutical sciences that have been discussed in this article. Before the advent of reasonably powerful computers and laser sources, the benefit of Fourier transform techniques as such and Raman spectroscopy in particular was questionable and, for a long time, its potential was badly underestimated. Today it is difficult to imagine a modern research laboratory without these techniques. For terahertz spectroscopy and imaging, with all its potential for rapid and non-destructive testing, the future is still to show whether it will develop into a niche application or become established widely in the pharmaceutical sciences.

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