

## TERAHERTZ SPECTROSCOPY

## Signatures and fingerprints

Terahertz technology seems set to become important in security screening and the pharmaceutical industry.

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**T**he ultimate solution for airport security would be a system that not only tells security staff if someone is hiding something under their clothes, but can also identify what that object is. Today's systems are limited in their capabilities: metal detectors only detect metal, and X-ray machines are not suitable owing to risks associated with regular exposure to ionizing radiation and their inability to image many organic compounds. The answer may lie at the other end of the electromagnetic spectrum, in the terahertz region.

Terahertz technology makes it possible to perform imaging through clothes, and other materials such as paper or

plastics, and the data retrieved can then be spectroscopically analysed to thus identify any foreign objects that are present. The terahertz region of the spectrum, which is often called the far infrared, lies between the mid-infrared and microwave regions. It has remained largely unexplored until recently because generating and detecting radiation in this frequency band was complicated and difficult (see Box 1).

Historically, experiments in the terahertz region have been performed by Fourier-transform interferometry using radiation from a black-body source and a bolometer cooled to very low temperatures as a detector. Although this is an unwieldy and inefficient method, it was useful for the investigation of fundamental topics, such as the rotational vibrations of gas molecules.

Technology has now moved on, and it is now possible to generate continuous-wave terahertz radiation by exposing a semiconductor to beams from two infrared

laser diodes that are very close in frequency. Emission is then obtained at the difference frequency of the lasers, and this can be engineered to fall in the terahertz range.

Terahertz spectroscopy has some important differences when compared with conventional infrared spectroscopy. Whereas the absorption of infrared radiation in a solid is typically due to the excitation of vibrational modes of the intramolecular bonds, terahertz waves are lower in energy and excite longer-wavelength vibrations, such as the phonons in a semiconductor crystal or molecular vibrations in an organic material. These molecular vibrations are a unique and distinct signature of a material, and thus terahertz spectroscopy is an important tool in identifying different substances, especially when those substances are obscured by clothing or other materials.

Pulsed terahertz spectroscopy and its use for security applications has been

### Box 1 Generation and detection of terahertz radiation

The terahertz region of the electromagnetic spectrum between 0.2 THz and 2 THz has been neglected for a long time. The reason is simple: lower frequencies can be generated by the rapid transport of electrons in semiconductors, but severe difficulties occur when frequencies rise to near the terahertz range, 0.1–2.0 THz. Frequencies above 1 THz can now be generated by direct conversion of electrical to optical power, but it is necessary to cool the source to temperatures near that of liquid helium, a considerable disadvantage for a practical system. Much higher frequencies in the near-infrared and visible regions can be obtained in many types of semiconductor lasers or LEDs that exploit a direct energy gap in a semiconductor.

The situation regarding generation of terahertz radiation changed in the 1980s when lasers producing femtosecond pulses became available. David Auston and colleagues at Bell Laboratories in the USA showed that illuminating a semiconductor

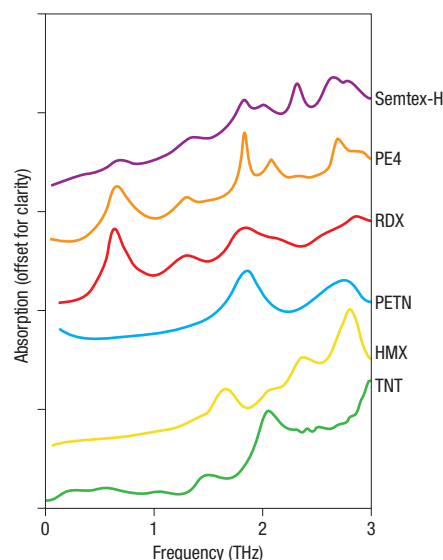
with a near-infrared pulse that had a duration of around 100 femtoseconds resulted in the semiconductor emitting a burst of terahertz radiation. The basic mechanism is that the infrared pulse induces free carriers and a rapidly rising current, which then collapses when the infrared pulse terminates. As with the generation of radio signals, the net effect of a change of current is the emission of radiation, in this case in the terahertz region of the spectrum.

Detection is by an inverse mechanism. The terahertz radiation falls on a semiconductor, which is simultaneously excited by light tapped off from the same infrared pulse that generates the terahertz radiation. This method of coherent detection is used at room temperature and is extremely sensitive. (Signal-to-noise ratios of  $10^5$  can be obtained at 1 THz.) Another method of producing terahertz waves is to use the nonlinear optical properties of some materials, which results

in a mixing of wavelengths in the infrared pulse to produce terahertz emission. Typical terahertz systems produced by TeraView offer frequencies in the range 0.05–3.5 THz with a pulse repetition rate of 80 MHz.

Spectroscopy is based on Fourier analysis of the time dependence of the reflected pulse, which gives the absorption as a function of frequency. Traditional spectroscopy was based on analysis of the transmitted radiation, but now it is possible to perform analysis using the reflected radiation, and a number of sophisticated techniques, such as attenuated total reflection, have been developed.

Safety aspects of terahertz radiation have been investigated, but no hazards have been found so far. The power levels are much less than those due to mobile phones and the radiation frequency is too low to cause ionization. Excitation of specific lattice vibrations in DNA has been shown to be ineffective in producing any potentially harmful structural change.

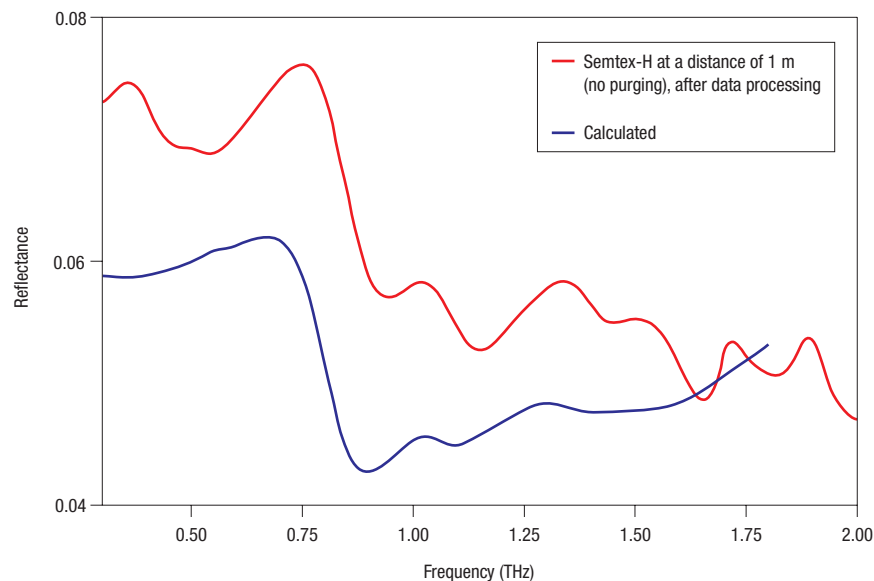


**Figure 1** Different explosives have unique terahertz spectral fingerprints, shown here by spectra obtained for some common explosive materials using a terahertz spectrometer working in reflection mode. The explosives include: (2,4,6)-trinitrotoluene (TNT), cyclotetramethylene tetranitramine (HMX), pentaerythritol tetranitrate (PETN) and cyclo-1,3,5-trimethylene (RDX). Also, shown are the spectra for two commercial plastics explosives: PE4 and Semtex-H are trade names.

investigated by many institutions and research groups around the world, and terahertz absorption spectra of common pure explosives and commercial plastic explosives have now been obtained. Most common explosives have characteristic absorption lines in the range 0.2–3.0 THz, and these can be investigated even when covered by clothes or paper, which have no spectral lines in this region.

As a particular spectroscopic signature is unique to an individual compound, it is possible to determine if a ‘white powder’ is an explosive or a harmless entity, even in the presence of ‘confusion materials’ that have a similar visual appearance. Similar considerations apply to narcotics. Figure 1 shows the spectra obtained for some common explosive materials.

In many operational settings, it is desirable to acquire terahertz spectra at a distance from the equipment (emitter and receiver). For example, this would be the case for a security scanner in airports with people walking through a portal similar to present-day metal detectors. At TeraView we have developed a stand off (remotely located) spectrometer. Figure 2 shows a spectrum of Semtex explosive taken from a distance of 1 metre. In most environments water vapour will give rise to numerous



**Figure 2** A spectrum of Semtex-H explosive taken at a distance of 1 metre from the emitter and detector. The good agreement of the main features with those predicted by theory is apparent.

absorption lines, but these can be removed by appropriate software.

Active terahertz imaging will probably have a significant contribution to make in future surveillance systems. That said, security applications are not the only attractive possibility for terahertz imaging and spectroscopy. The technology also has huge potential in medical and pharmaceutical markets.

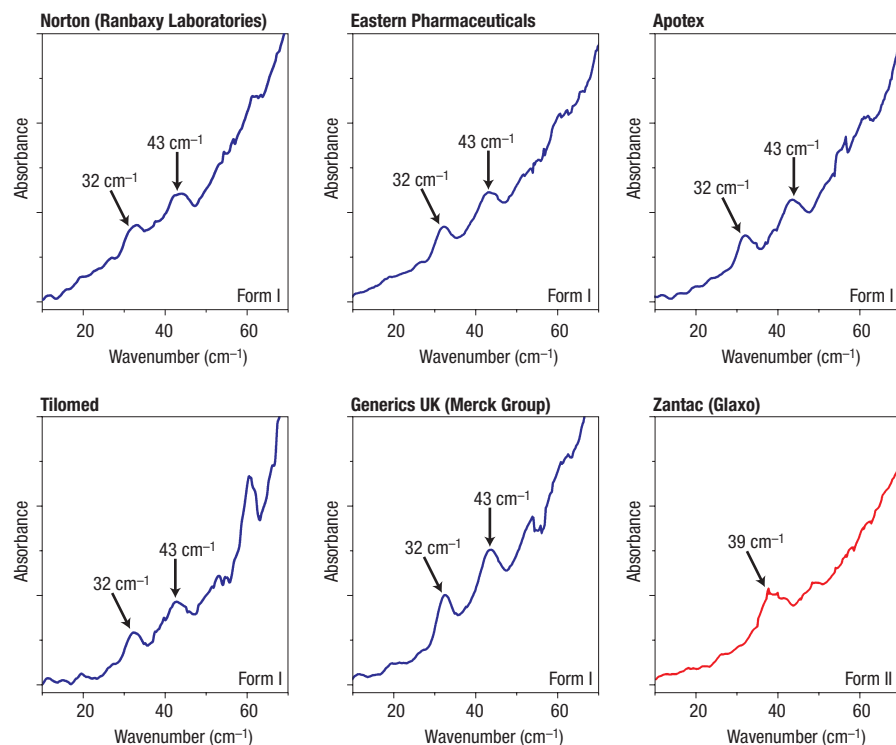
Considerable research is taking place into the medical applications of terahertz technology following successful imaging of tumours in skin and breast tissue. A benefit of this approach is that it does not involve ionizing radiation. However, the limited penetration depth of terahertz waves in tissue (they are strongly absorbed by water) prevents whole-body imaging, which is an attractive feature of X-ray or magnetic resonance imaging.

Interestingly, tissue does not have any particular spectroscopic signature but rather a broad absorption, which increases with energy owing to the high water content. Tumorous tissue has both a higher absorption and higher refractive index, but is also devoid of any structure as a function of frequency. These differences in optical properties enable a very clear identification of tumorous tissue by reflection imaging. In fact, for some types of tumour in breast tissue terahertz radiation has been shown to be more discriminating than X-rays. At present terahertz marker molecules, which attach to tumours, have not been investigated, and future potential applications are imaging during surgery and endoscopy.

Because it is a non-invasive technique, terahertz spectroscopy is also making a considerable impact on the pharmaceutical industry. Measurements can be used for in-line monitoring of products such as tablets during manufacture, as well as proving useful for product development.

Drug polymorphism (a phenomenon in which compounds exhibit the same chemical composition but have a different lattice structure), polymorphic conversion and dehydration behaviour are all issues of paramount importance to the pharmaceutical industry. These phenomena occur frequently in formulation development, production of solid dosage forms or storage, and may have therapeutic, commercial and legal implications, as the effects of the tablet in the body may change. Because terahertz spectroscopy probes directly at the intermolecular vibrations (lattice phonon modes) it is ideal for detecting and monitoring solid-state crystalline properties.

Some of the drug compound polymorphisms that have been investigated include polymorphic forms I and III of carbamazepine (an anticonvulsant and mood-stabilizing drug), as well as all the polymorphic forms of sulfathiazole (an antibiotic). Sulfathiazole is a classic polymorphic system that has been studied extensively over the past 60 years. Its different forms are not easily discerned using traditional characterization methods, such as X-ray powder diffraction or differential scanning calorimetry. Previously confirmation using a second technique such as nuclear magnetic



**Figure 3** Terahertz spectroscopy on whole tablets of ranitidine hydrochloride — a treatment for indigestion and heartburn. It has two polymorphic forms that are bioequivalent, but form II is cheaper to manufacture. Out of all the products tested with terahertz pulsed spectroscopy, only Zantac from GlaxoSmithKline contained ranitidine polymorphic form II.

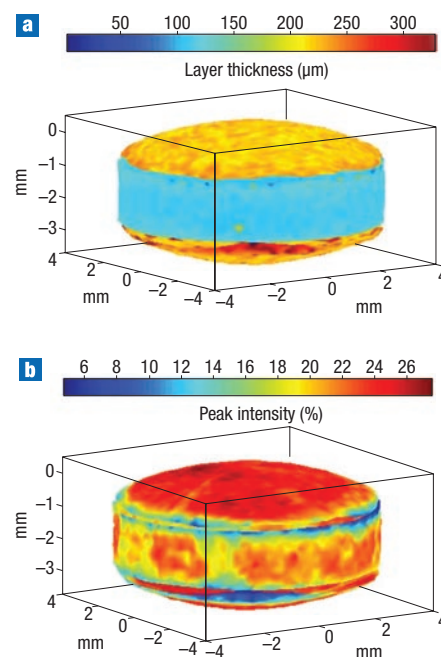
resonance imaging was necessary. Clearly the use of such techniques is acceptable in a lengthy research investigation, but is not compatible with rapid inspection. In comparison, the spectral signatures of all five polymorphic forms of sulfathiazole can be easily distinguished in the terahertz region with an acquisition time per spectrum of less than 100 milliseconds.

Although much research into polymorphic identification is carried out on powder samples compressed into pellets, polymorphic detection is also easily achieved while the drug is in a solid dosage form, such as in a whole tablet. As an example, ranitidine hydrochloride was investigated. This compound exists in two polymorphic forms: I and II. They are bioequivalent; however, form II is cheaper to manufacture, hence it is used as the active pharmaceutical compound in the product Zantac, a treatment for indigestion and heartburn marketed by GlaxoSmithKline. A range of generic tablets were tested as well, and the results were compared with the spectroscopic data obtained from the raw material. These tests showed that polymorphic form II has a spectral peak at  $39\text{ cm}^{-1}$ . Spectral peaks at  $32\text{ cm}^{-1}$  and  $43\text{ cm}^{-1}$  are signatures for form I. As seen

in Fig. 3, which are the results of terahertz spectroscopy on complete tablets, all generic products contained polymorphic form I, and only Zantac contained form II. The use of spectroscopy is sufficiently reliable that the actual drug polymorph concentration can be determined at concentrations as low as 1.5%.

Terahertz spectroscopy has been shown to be capable of monitoring the rapid processes of polymorphic conversion and dehydration behaviour, as high-quality spectra from many points on a tablet can be rapidly obtained. Production operations can exert a force or thermal strain on the drug, which may cause changes in its crystalline structure. A real-time observation of polymorphic transformations in carbamazepine was monitored successfully. Clear evidence of two co-existing polymorphic forms was found, with the complete conversion to one form as the temperature increased.

Apart from spectroscopy, terahertz radiation can also be useful for imaging tablet film coatings. Tablet film coating is carried out to improve the physicochemical properties of tablets for cosmetic or therapeutic purposes. Accurate detection of film-coating defects is imperative for improving production processes and



**Figure 4** Terahertz pulsed imaging of film coatings. A desirable penetration depth into the tablet film coating can be achieved using terahertz pulsed imaging, which enables the construction of accurate three-dimensional tablet models for assessing variations in, **a**, film-coating thickness and, **b**, density.

predicting dissolution performance. As a result of the transparent or semitransparent nature of most pharmaceutical excipients (inert filler materials used in drugs to provide bulk) in the terahertz region, terahertz pulsed imaging can penetrate most solid dosage forms to a depth of up to 3 mm, enabling non-destructive analysis of the film coating (Fig. 4). The technique has demonstrated potential in predicting the dissolution performance and as a process analytical tool for improving the manufacture of film coatings.

At present, terahertz imaging and spectroscopy are two separate functions, but future developments will combine the two for a full three-dimensional physicochemical mapping of solid dosage forms. Technology is also now being developed for the in-line monitoring of products during manufacture, and terahertz spectrometers and imagers will be important in the research and formulation stages of the development of future products.

Terahertz spectroscopy has developed enormously since the introduction of pulsed techniques. It is not only of benefit in basic research investigations, but is playing a role in the understanding of industrial processes, a role that will increase with time.