DRUG INVENTION TODAY 5 (2013) 157–163

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Review Article

Terahertz technology and its applications

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ARTICLE INFO

Article history:
Received 17 January 2013
Accepted 31 March 2013

Keywords:
Terahertz
Spectroscopy
THz
Radiation
Frequency

ABSTRACT

New advances in different technologies have made the previously unused terahertz frequency band accessible for imaging systems. The 'terahertz gap' has a frequency ranges from ~0.3 THz to ~10 THz in the electromagnetic spectrum which in between microwave and infrared. The terahertz radiations are invisible to naked eye & in comparison with X-ray they are intrinsically safe, non-destructive and non-invasive. This is such a new field that researchers around the world race to build the first practical system. It resolves many of the questions left unanswered by complementary techniques, such as optical imaging, Raman and infrared. Terahertz spectroscopy has number of applications run from detecting defects in tablet coating, product inspection (industry), spectroscopy (chemistry, astronomy), material characterization (physics), weapons concealed under clothing (airports), detection of cancer and caries. In the pharmaceutical industries it enables nondestructive, internal, chemical analysis of tablets, capsules and other dosage forms. This paper tries therefore not only to provide a brief overview over the imaging technology, but also over the whole range of current systems and research in terahertz technology.

1. Introduction

Terahertz radiation falls in between infrared radiation and microwave radiation in the electromagnetic spectrum and it shares some properties with each of these. Like infrared and microwave radiation, terahertz radiation travels in a line of sight and is non-ionizing. Like microwave radiation, terahertz radiation can penetrate a wide variety of non-conducting materials. Terahertz radiation can pass through clothing, paper, cardboard, wood, masonry, plastic and ceramics. The penetration depth is typically less than that of microwave radiation. Terahertz radiation has limited penetration through fog and clouds and cannot penetrate liquid water or metal.[1]

In physics, terahertz radiation, also called submillimeter radiation, terahertz waves, terahertz light, T-rays, T-waves, T-light, T-lux, or THz, consists of electromagnetic waves at frequencies from 0.3 to 10 terahertz (THz). The term applies to electromagnetic radiation with frequencies between the high-frequency edge of the millimeter wave band, 300 GHz and the low frequency edge of the far-infrared light band, 3000 GHz. Corresponding wavelengths of radiation in this band range from 1 mm to 0.1 mm (or 100 μm).[2] Because terahertz radiation begins at a wavelength of 1 mm and proceeds into shorter

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0975-7619/$ – see front matter
http://dx.doi.org/10.1016/j.dit.2013.03.009

wavelengths, it is sometimes known as the submillimeter band and its radiation as submillimeter waves, especially in astronomy.

The earth's atmosphere is a strong absorber of terahertz radiation in specific water vapor absorption bands, as seen in Fig. 1, so the range of terahertz radiation is limited enough to affect its usefulness in long-distance communications. However, at distances of ~10 m the band may still allow many useful applications in imaging and construction of high bandwidth wireless networking systems, especially indoor systems.[3] In addition, producing and detecting coherent terahertz radiation remains technically challenging, though inexpensive commercial sources now exist in the 300–1000 GHz range (the lower part of the spectrum), including gyrotrons, backward wave oscillators, and resonant-tunneling diodes.

Terahertz radiation occupies a middle ground between microwaves and infrared light waves, and technology for generating and manipulating it is in its infancy and is a subject of active research (Fig. 1). It represents the region in the electromagnetic spectrum in which the frequency of electromagnetic radiation becomes too high to be measured by directly counting cycles using electronic counters, and must be measured by the proxy properties of wavelength and energy.

Similarly, in this frequency range the generation and modulation of coherent electromagnetic signals ceases to be possible by the conventional electronic devices used to generate radio waves and microwaves, and requires new devices and techniques. The electromagnetic range that is used is very vast. At low frequencies end we have radio waves up to millimeter waves, and at the other end we have optical waves down to the far infrared. Technologies have been developed for both ends of the spectrum which we use in everyday applications. But the terahertz region:

$$0.3 - 10\ \text{THz},\ \ 1\ \text{THz} = 1012\ \text{Hz}$$

with wavelength of 30 μm–3 mm has remained largely underdeveloped, despite the identification of various applications, in particular terahertz imaging and others which will be discussed later on.

It is possible to produce effectively radiation in the low frequency region (microwaves) with oscillating circuits based on high-speed transistors and at high frequencies (visible spectrum) with semiconductor lasers. But transistors and other electric devices based on electric transport have in principle a limit at about 300 GHz, but are practically limited to about 50 GHz, because devices above this are extremely inefficient[1–3] and the frequency of semiconductor lasers can only be extended down to about 30 THz. Thus there is a region in between where both technologies do not meet. This region is often referred to as the terahertz gap.

Terahertz radiations have a few remarkable properties. Many common materials and living tissues are semi-transparent and have 'terahertz fingerprints', permitting them to be imaged, identified and analyzed. Due to non-ionizing properties of terahertz radiations are safe for screening application. These unique properties of radiations are now exploited due to availability of commercial sources of terahertz radiations.[3]

2. Sources of terahertz radiation[4,5]

2.1. *Natural*

Terahertz radiation is emitted as part of the black-body radiation from anything with temperatures greater than about 10 K.[4] While this thermal emission is very weak, observations at these frequencies are important for characterizing the cold 10–20 K dust in the interstellar medium in the Milky Way galaxy, and in distant starburst galaxies.

2.2. *Artificial*

The viable sources of terahertz radiation are[4,5]:

- The gyrotron
- The backward wave oscillator ("BWO")
- The far infrared laser ("fir laser")
- Quantum cascade laser
- The free electron laser (Fel)
- Synchrotron light sources
- Photomixing sources
- Single-cycle sources used in terahertz time domain spectroscopy such as photoconductive, surface field, photo-Dember and optical rectification emitters
- A new source was developed that used a resonant tunneling diode (RTD) in which the voltage decreased as the current increased, causing the diode to "resonate" and produce waves in the terahertz band at 542 GHz

2.3. *THz frequency spectroscopy*

Since the first use of femtosecond lasers to generate coherent THz frequency radiation, there has been a drive to develop

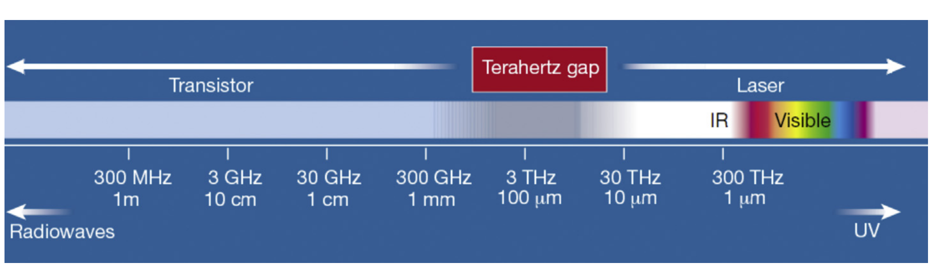

Fig. 1 – The terahertz gap.

higher power sources and systems of broader bandwidth. A number of techniques have been explored, including bulk electro-optic rectification, surface field generation and ultrafast switching of photoconductive emitters. Of these different methods, photoconductive emitters have proved to be the most efficient technique for converting visible/near-IR pulses to THz radiation, and have been widely used for THz spectroscopy and imaging.[6] In this technique, electron–hole pairs are generated in a semiconductor crystal using an above-band gap femtosecond pulse, and these photo excited carriers are then accelerated by an applied electric field. The photo excited carriers constitute a transient current pulse, which emits THz radiation in accordance with Maxwell's equations. Fig. 2 shows a typical experimental THz – Time domain spectroscopy (TDS) arrangement for coherent generation and detection of broad bandwidth THz radiation. Although the experimental details vary between different systems, in this example the emitter comprises two vacuum-evaporated NiCr/Au electrodes separated by a submillimeter-wide gap, fabricated on a 1-μm-thick, low-temperature-grown (LT) GaAs layer, itself grown on an undoped GaAs substrate. Suitably annealed LT-GaAs is an ideal material for this application, providing short photo carrier recombination lifetimes (a few hundred femtoseconds), together with both high resistivity (which allows high electric fields to be used) and high carrier mobility.[7] A bias voltage of around ±100 V, modulated at a few kilohertz, is applied across the emitter electrodes. A pulsed Ti:sapphire laser beam, typically of a few hundred mill watts average power (~10–100 fs pulse width, 800 nm center wavelength) is focused onto the edge of one of the two electrodes, and THz pulses are generated as described above. In this arrangement, pulses with a usable bandwidth extending to ~3 THz are typically obtained.

2.3.1. *Sample preparation*

In terahertz spectroscopy, as in Fourier transform infra-red spectroscopy (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 (tetrafluoroethylene) (PTFE) are transparent to terahertz radiation and are therefore typically used as diluent materials. Depending on the absorption coefficient of the sample, between 5 and 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 mm 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 echeloning arte facts in the recorded spectra.[6,7]

Alternatively, if the sample material compacts well like tablet, 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.[8]

Among other gases, atmospheric water vapor exhibits a very strong rotational spectrum in the terahertz range. Compared with the terahertz spectra of solids, the peaks observed in the rotational spectra are, in general, more intense and very narrow.[9] Consequently, they can be easily distinguished from spectral signatures of solid materials. To minimize the contribution of the water vapor to the sample spectrum, the sample chamber is either purged with dry nitrogen or evacuated throughout the measurements.

3. Applications

3.1. *Pharmaceutical industry: tablet integrity and performance*

Coating has a wide variety of functions. The most important function of coating is to regulate the controlled release of active ingredients in the body. Coating not only contributes to

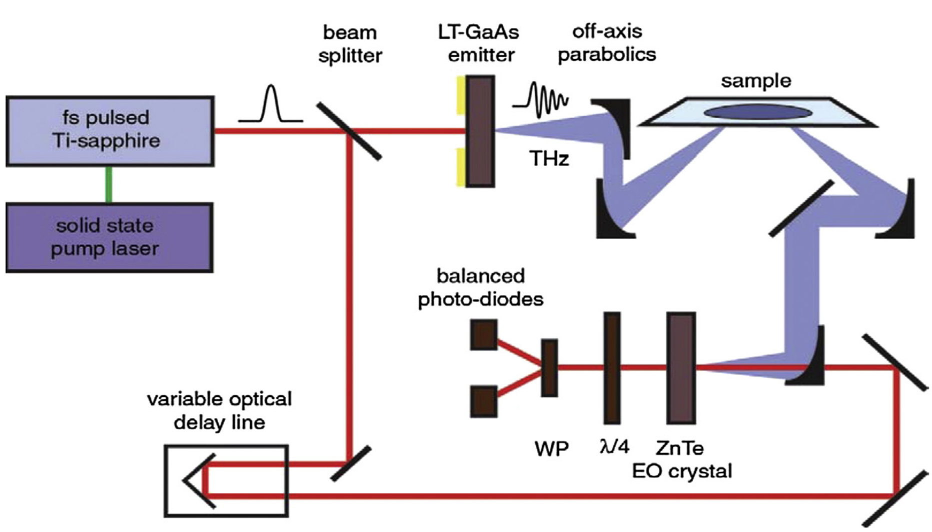

Fig. 2 – Schematic of a THz-TDS system. In this example, the THz pulses are generated by a low-temperature-grown (LT)-GaAs photoconductive switch and subsequently detected, after reflection off the sample, by electro-optic sampling using a ZnTe electro-optic crystal [6].

the bioavailability of a particular drug or combination of drugs during certain times and locations but also coating can protect the stomach from high concentrations of active ingredients, improve tablet visual appeal and extend shelf life by protecting the ingredients from degradation by moisture and oxygen.[10] In relation to tablet coating the process analytical technology (PAT) initiative is intended to improve consistency and predictability of tablet action by improving quality and uniformity of tablet coatings. Issues with coating can arise from problems with the coating materials or flaws in the coating pan or spray process. If a coating is non-uniform or has surface defects then the desired dose delivery and bioavailability can be compromised. From this standpoint it is important to characterize tablet coating uniformity, both within a single tablet and across an entire batch to develop an understanding of the functional analysis of the final product. Several analytical and imaging techniques are being used to understand the critical processes involved in tablet coating but none of them is ideal to fully characterize the layers. Some of the techniques that provide useful information are atomic force microscopy, confocal laser microscopy, X-ray photoelectron spectroscopy, electron paramagnetic resonance, Fourier transform infrared spectroscopy, and laser induced breakdown spectroscopy (LIBS) and scanning thermal microscopy. However all these methods are either destructive to the tablet or cannot be readily implemented for rapid on-line measurement.[11]

Terahertz image can be optimized for performing 3D analysis on tablets. It can enable to determine coating integrity and thickness, detect and identify localized chemical or physical structure such as cracks or chemical agglomeration within a core and to interrogate embedded layers (such as an interface between two layers) for delamination and integrity. Terahertz measurements may well become the primary method for the nondestructive determination of coating thickness, requiring little or no calibration for most coatings and substrates.[12] It can reveal the thickness, uniformity, distribution and coverage of simple and complex coating. Terahertz image can also detect embedded layers and localized chemical or physical structural features in the cores of intact tablets to confirm 3D morphology and blend uniformity.

3.1.1. *Terahertz pulsed imaging (TPI)*

TPI is a completely non-invasive and non-destructive pharmaceutical analysis tool using extremely low power, ultra short pulses of electromagnetic radiation at lower frequencies than infrared (1 THz = 1012 Hz).[12] Terahertz spectroscopy has already proved useful to distinguish between different polymorph forms of the drug.[13] TPI is a next step of this whereby THz pulses are used to image object of interest. THz pulses are generated by illuminating photoconductive semi-conductors with pulsed near-infrared laser radiation and detected coherently.[14] Tablet coatings are semi-transparent to THz frequencies and do no scatter them significantly. THz pulses incident on a tablet surface penetrate through the different coating layers. At each interface a portion of THz radiations is reflected back to the detector. The amplitude of reflected THz radiation is recorded as a function of time. In this technique the sample itself is completely unaffected by the measurement.[15] Coating thickness uniformity is established simply from the transit time of the pulse to each interface. With knowledge of the refractive index of coating material the actual thickness can be determined to a depth resolution of about 20 microns. The spot size of the THz pulse, and therefore lateral resolution, is about 250 microns.[16]

3.2. *Molecular structure*

The sensitivity and specificity of terahertz spectroscopy to both intermolecular and intramolecular vibrations in different chemical species enable investigation of the crystalline state of drugs e.g. Polymorphism. The use of pulsed terahertz imaging in proteomics and drug discovery determines protein 3D structure, folding and characterization.[17] It is also very sensitive to DNA hybridization and other interactions. Terahertz spectroscopy provides rapid identification of the different crystalline forms of drug molecules – the polymorphs – which can exhibit different solubilities, stabilities and bioavailability and hence are an important factor in the therapeutic efficacy of a drug. Detecting and identifying the different polymorphs and understanding the mechanism and dynamics of polymorphic inter-conversion, is an important milestone in selecting the optimum form for further development and manufacture.[18] It is possible not only to detect the differences between pure specimens of the polymorphs but terahertz spectroscopy can distinguish between specific polymorphic forms in tablet formulation.

Terahertz spectroscopy can also differentiate between different hydrate forms. Lactose which is one the most commonly used excipients in the pharmaceutical industry has at least three different hydrates namely α-monohydrate, α-anhydrate and β-anhydrate form.[19,20] These three hydrate forms exhibit terahertz spectra that can be used for both quantitative and qualitative analysis (Fig. 3). Terahertz region provides unique sensitivity to lattice structure enabling qualitative and qualitative analysis of crystalline and amorphous materials as well.

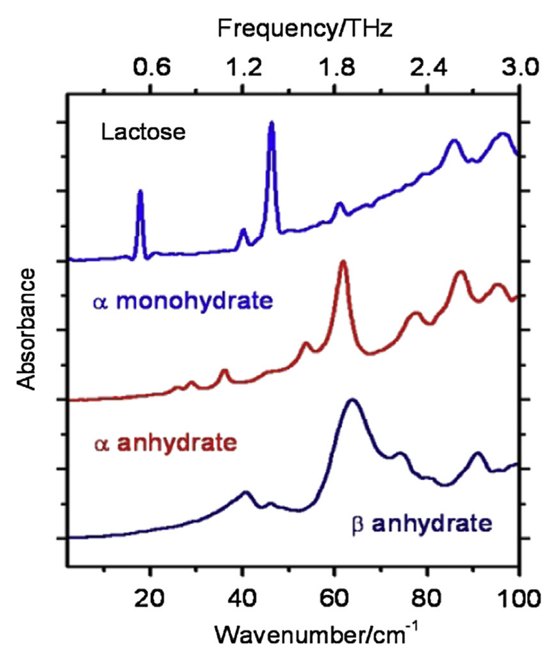

Fig. 3 – Terahertz spectroscopy to differentiate hydrate forms of Lactose.

3.3. Time resolved THz spectroscopy of protein folding

Proteins fold, catalyze reactions, and transducer signals via binding to other biomolecules. These processes are driven by motions with characteristics time scales ranging from femtoseconds (fs) to milliseconds (ms).[21] The characteristic modes from which such motions collectively emerge often cause large amplitude deformations of all or part of the protein. Temperature tuning reveals when certain modes are frozen out, while the terahertz spectroscopy can cover fast relaxation kinetics on fs time scale during which a protein rearranges its overall structure.

3.4. In dermatology

The cosmetic appearance of skin is directly linked to the outermost layer, the stratum corneum. The water content of the stratum corneum influences its permeability and elasticity. Most skin-care products such as moisturizers act to increase the retained water content of this layer of the skin to enhance its appearance. Quantitative characterization of the hydration level of the stratum corneum is thus of crucial importance to the cosmetic industry in order to characterize and compare the effectiveness of their products.[22]

Basal cell carcinoma (BCC) is the most common form of cancer worldwide in white populations and has a reported annual incidence of over 1 million in the U.S.A.[22,23] Several different imaging techniques are being evaluated as diagnostic tools for skin lesions and tumor margin assessment. The terahertz (THz) frequency wavelength is of particular interest as it excites the intermolecular interactions, such as the librational and vibrational modes of molecules providing spectroscopic information. Terahertz pulse imaging (TPI) is a noninvasive, coherent optical imaging modality that explores this frequency region. These wavelengths are significantly larger than the scattering structures in tissue; therefore we assume that scattering effects are negligible. The current lateral and axial resolutions attainable with our system at 1 THz are 350 m and 40 m, respectively, making it a viable imaging modality.[23] As TPI is a coherent, time gated, low noise technique, both phase and amplitude information can be obtained, from which the absorption and refractive index of a medium can be determined. This enables TPI to provide both structural and functional information, due to chemical specificity. Through examination of the terahertz waveform in both the time and frequency domains, TPI may prove advantageous in distinguishing type, lateral spread, and depth of tumors.

3.5. Oral healthcare

Dental carries or tooth decay is one of the most common human disorders. Carries proceed by the creation of a subsurface lesion in the enamel. The lesion may extend to the next tissue in the layer in teeth, the dentine, without macroscopically visible breakdown or even microcavity formation at the tooth surface. The absence of visual features on the tooth surface makes early detection of tooth decay difficult.[23] X-rays which is one of the accepted methods used to detect decay, only reveals the problem at a relatively late stage, when drilling and filling is the only method available to halt the decay. If decay can be detected early enough it is possible to reverse the process without the need for drilling by the use of either fissure sealing or remineralization.[24]

Terahertz imaging can distinguish between the different types of tissue in a human tooth; detect carries at an early stage in the enamel layers of human teeth and monitor early erosion of the enamel at the surface of the tooth.

3.6. Oncology

It is estimated that more than 85% of all cancers originate in the epithelium. Excision biopsy to remove tissue from the body and examining it under a microscope is the gold standard for cancer diagnosis. Terahertz technology has the potential to greatly improve conventional biopsy and associated surgery by more precisely identifying the areas to be excised thereby reducing the number of procedures and facilitating earlier and more accurate diagnosis.[24] As the technology develops, it may be possible to perform biopsies using live terahertz imaging of affected area, making possible point of care optical biopsy.

3.7. Detection of impurities in pharmaceutical industry

The manufacturing of pharmaceutical products is a highly monitored process that requires strict quality regulations. If the final product fails to meet the standard set by regulatory agencies then the whole batch is destroyed. This encourages the pharmaceutical industry to work on batch-processing techniques. Typically, pharmaceutical companies manufacture a finished product and then use laboratories to analyze a proportion of the batch to verify the quality of their product. Terahertz radiation has the ability to obtain information on chemical and physical structures and is able to accomplish this in real-time in a non-destructive form. This shows potential for the pharmaceutical industry as it is able to specifically determine the structure and properties of the sample to test, such as the bioavailability, manufacturability, purification, stability, dissolution rate, solubility and other performance characteristics of the drug. During manufacturing, solid pharmaceutical materials may come into contact with water or other impurities during processing, which can affect the product performance. THz Spectroscopy can measure the unique physico-chemical properties of a product, being able to specifically distinguish one product from another which provides quality information.[25] Terahertz Spectroscopy can also be used to patent pharmaceutical products because of the ability to distinguish the specific chemical components.

3.8. Medical imaging

Contrary to X-rays, terahertz radiation has a relatively low photon energy for damaging tissues and DNA. Some frequencies of terahertz radiation can penetrate several millimeters of tissue with low water content (e.g., fatty tissue) and reflect back. Terahertz radiation can also detect differences in water content and density of a tissue.[26] Such methods could allow effective detection of epithelial cancer with an imaging system that is safe, non-invasive, and painless.

Spectroscopy in terahertz radiation could provide novel information in chemistry and biochemistry. Recently

Fig. 4 – Terahertz image of men with hidden knife.[33]

developed methods of THz time-domain spectroscopy (THz TDS) and THz tomography have been shown to be able to perform measurements on, and obtain images of, samples that are opaque in the visible and near-infrared regions of the spectrum.[27] The utility of THz-TDS is limited when the sample is very thin, or has a low absorbance, since it is very difficult to distinguish changes in the THz pulse caused by the sample from those caused by long-term fluctuations in the driving laser source or experiment. However, THz-TDS produces radiation that is both coherent and spectrally broad, so such images can contain far more information than a conventional image formed with a single-frequency source.[28]

3.9. *Security*

Terahertz radiation can penetrate fabrics and plastics, so it can be used in surveillance, such as security screening, to uncover concealed weapons on a person, remotely.[29,30] This is of particular interest because many materials of interest have unique spectral “fingerprints” in the terahertz range. This offers the possibility to combine spectral identification with imaging. Passive detection of terahertz signatures avoids the bodily privacy concerns of other detection by being targeted to a very specific range of materials and objects.

At airports or other security critical places dangerous nonmetallic substances like ceramic knifes or plastic explosives now can be detected with terahertz beams.[31–33] This is possible because T-rays get through clothes, but cannot get through the upper skin (because of the water content). Fig. 4 illustrates very clear how effective this imaging method works.

3.10. *Communication*

Potential uses exist in high-altitude telecommunications, above altitudes where water vapor causes signal absorption: aircraft to satellite, or satellite to satellite.[34]

4. Conclusion

Terahertz frequency radiation possesses a unique combination of desirable properties for noninvasive imaging and spectroscopy of materials. Terahertz spectroscopy is of prime importance for tablet coating technology. Most important advantage of terahertz technology is that it is nondestructive method of analysis. Tablets can be re-examined at later times to monitor coating stability or used for further functional studies with prior knowledge of the coating uniformity. The applications mentioned here show that THz imaging is desired by many different parts of industry and research, so that it can be expected that much effort will go into this field. But despite the number of potential applications for THz imaging no technology is yet the ideal way, though the recent advances could lead to practicable and compact systems. Hence, research in this field is going to be very lively and interesting in the future.

Conflicts of interest

All authors have none to declare.

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