

Inspection of Solid Dosage Forms using THz Imaging Spectroscopy

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Abstract — The present work describes a laboratory terahertz (THz) imaging spectroscopy system and its possibilities to inspect solid dosage forms in the form of coated tablets and capsules. Moreover, the chemical composition and layer structure of coated pharmaceutical tablets are investigated. These chemical and physical properties of solid dosage forms can be used for the detection of counterfeit drugs. Preliminary results show that THz time domain spectroscopy and imaging is a promising technology for contactless control and analysis of pharmaceutical drug materials and final dosage forms.

Keywords - terahertz; imaging; spectroscopy

I. INTRODUCTION

Recent developments in THz instrumentation in combination with a better understanding of the mechanisms behind the interaction of THz radiation and materials made THz spectroscopy and especially THz spectroscopic imaging promising technologies for a wide range of applications. According to the World Health Organization (WHO), in 2006 the market for counterfeit drugs worldwide was estimated at around 43 billion USD. Moreover the WHO says that 50% of all drugs bought from the internet are counterfeit [1]. Terahertz imaging and spectroscopy are technologies which have the potential to be employed to help regulatory authorities, law enforcement agencies and the industry screen for counterfeit drugs in the near future. Over the past few years terahertz technology has become a new tool for the physical characterization of solid materials [2]. Applications for THz imaging and spectroscopy include the measurement of coating thickness and uniformity in coated pharmaceutical tablets, structural imaging and 3D chemical imaging of solid dosage forms. Moreover, as drug packaging materials like plastics are transparent for THz radiation, drug compositions can be analyzed and identified through the packaging [3]. The present work describes a laboratory measurement system consisting of a state of the art femtosecond fiber laser based THz imaging spectrometer and its possibilities to detect counterfeit drugs in the form of coated tablets and capsules. The chemical composition and coating thickness are analyzed. The coating thickness or layer structure is besides the chemical composition an important criterion for the detection of counterfeit drugs. Preliminary results show that THz time domain spectroscopy and imaging is a promising technology

for contactless control and analysis of pharmaceutical drug materials and final dosage forms.

II. TIME-DOMAIN IMAGING SYSTEM

The measurements were carried out with a fast, time-domain, THz imaging spectrometer (ZOMEGA, USA) with a spectral range from 0.1 to 3.5 THz and with a spectral frequency resolution smaller than 5 GHz. A NIR femtosecond laser (Toptica, Germany) with a second harmonic wavelength of 780 nm, a pulse width shorter than 100 fs and an output power greater than 140 mW was used for the generation of the THz pulses. All test samples were measured in transmission mode and reflection mode. For image acquisition a two-axis imaging

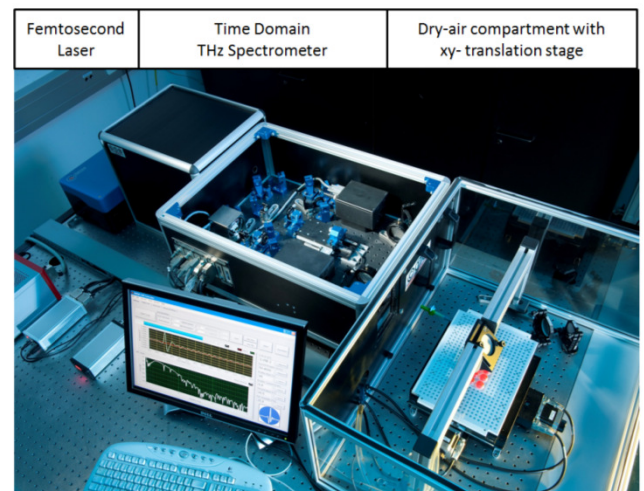


Figure 1: THz time-domain spectroscopy setup used to measure solid dosage forms in reflection geometry.

stage is used to perform rapid scans in reflection mode. A picture of the measurement setup is shown in Fig. 1. For this paper different types of coated tablets and capsules were analyzed for their chemical composition and 3D layer structure. The thickness and uniformity of the tablet coatings were measured in reflection mode with time-domain terahertz tomography while the chemical composition was measured with time-domain terahertz spectroscopy. The beam path inside the terahertz system is illustrated in Fig. 2.

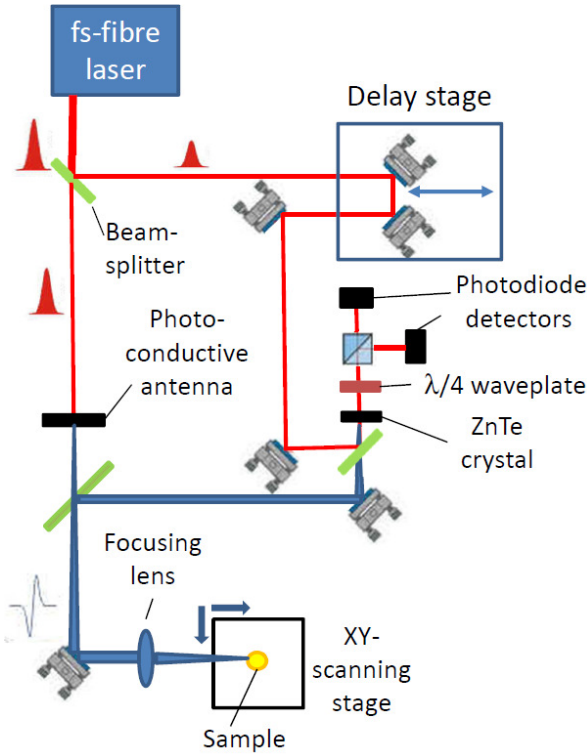


Figure 2: Laser beam path and THz beam path inside the measurement setup.

III. TIME-DOMAIN TERAHERTZ SPECTROSCOPY

Time-domain terahertz imaging can reveal spatially resolved information from below the surface of a sample. Most excipients used for solid dosage forms are transparent, or semi-transparent, to terahertz radiation. Hence it is possible for the terahertz pulse to penetrate into the sample. With terahertz pulsed imaging the information containing the layer structure of the sample is acquired in a single mapping scan from the surface of the sample. Reflections of the terahertz pulse from interfaces due to changes in the refractive indices between different layers inside the sample enable the reconstruction of the internal structure of the sample. The time delay of these reflections relative to the surface reflection is used to calculate the layer structure of the sample. In Fig. 3 a terahertz time-domain waveform of a coated tablet is shown. The first positive peak indicates the position of the air-to-coating interface. The second positive peak indicates the interface between the coating and the core of the tablet. The thickness of the coating can be determined by measuring the peak-to-peak distance (time delay) of the terahertz waveform. For this example the coating thickness is 100 μm . With the current setup a minimum coating thickness of approximately 50 μm can be measured. In Fig. 4 coatings of different thickness were measured and compared to ground truth. The measured coating thicknesses were 100 μm , 125 μm , 155 μm ,

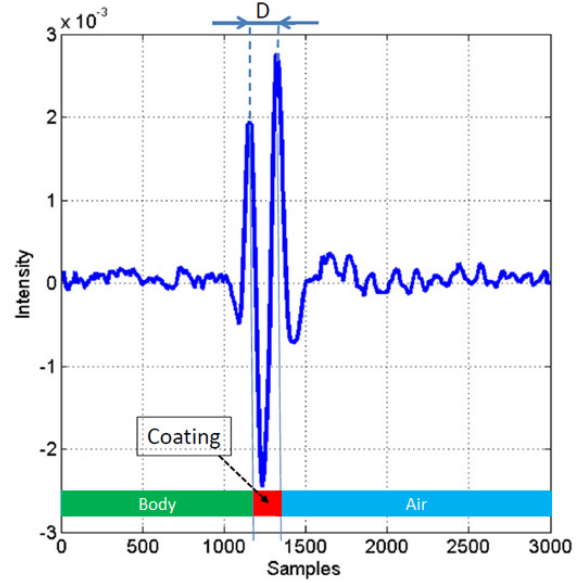


Figure 3: Time-domain THz tomography - THz response of a two layered material. The first positive peak indicates the position of the air-to-coating interface and the second positive peak indicates the position of the coating-to-body interface. The layer thickness of the coating corresponds to the distance between the two positive peaks. In this example the coating thickness was 100 μm .

200 μm , 285 μm , 310 μm , 355 μm , 420 μm , 450 μm , 700 μm and 850 μm . It can be seen that time-domain terahertz tomography can accurately measure the coating thickness. Moreover time-domain terahertz tomography can be used to visualize the spatial distribution of the coating thickness. In Fig. 5 a vertical cross-section of a coated tablet is shown. The two interfaces of the 100 μm thick coating layer are represented by the two horizontal structures. A two-dimensional mapping of the coating thickness over the whole tablet can be seen in Fig. 6. It is visible that the nominal coating thickness of 100 μm is not constant over the whole sample. The measurements for the coating thickness for this sample reach from 91 μm to 117 μm . Time-domain terahertz imaging can provide more information about the physical structure of a sample than only the layer thickness. The signal strength of the temporal waveform at an interface between two materials with different refractive indices contains useful information about the physical structure too. If the terahertz pulse propagates from a material with lower refractive index to a material with higher refractive index the temporal waveform will have a positive peak at this interface. And if the terahertz pulse propagates from a material with higher refractive index to a material with a lower refractive index the temporal waveform will have a negative peak at this interface. And also the peak amplitude of the temporal waveform is proportional to the difference of the refractive indices at this interface [4]. Beside the ability to measure the layer thickness of a solid dosage form, its coating uniformity and spatial

coating distribution, time-domain terahertz imaging can also detect structural defects within a tablet [5]. These structural defects are for example cracks and delaminations inside the

tablet and dislocations of tablet structures [3] [6]. Another advantage of terahertz radiation is its capability to penetrate most plastic sheet materials used for pharmaceutical blister packs. This makes it possible to analyze the coating structure of a tablet inside the sealed blister pack.

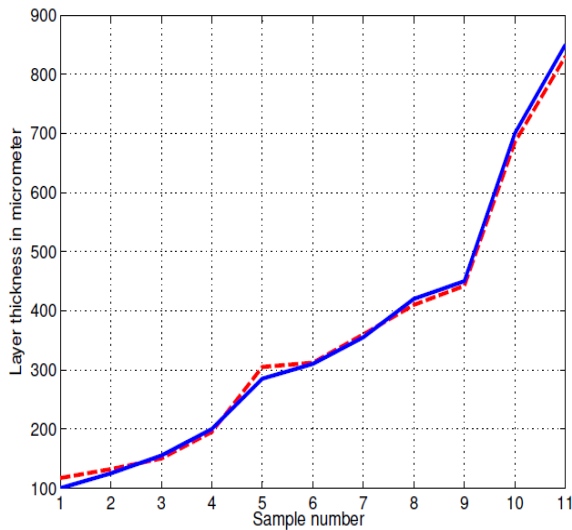


Figure 2: Time-domain THz tomography - The thickness of 11 different coatings were measured. The measured coating thicknesses were 100 μm , 125 μm , 155 μm , 200 μm , 285 μm , 310 μm , 355 μm , 420 μm , 450 μm , 700 μm , 850 μm , respectively. The blue solid line shows the ground truth of the layer thickness and the red-dashed line shows the actual THz measurements.

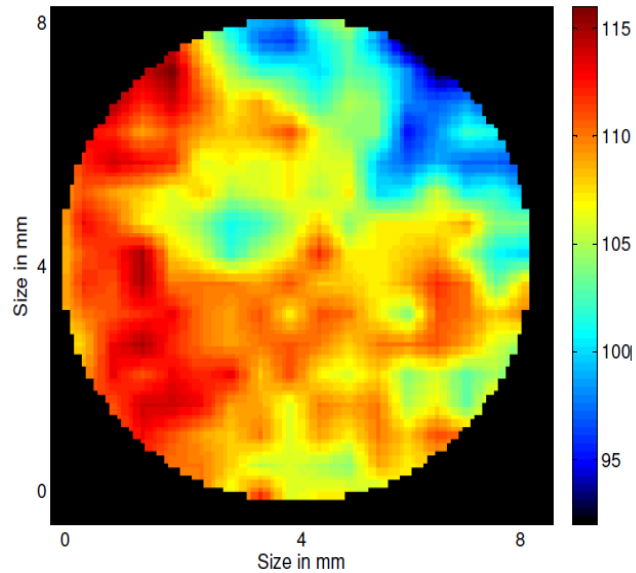


Figure 4: Time-domain THz tomography - 2D distribution of coating thickness across the sample. The measurements of the coating thickness vary in the range from 91 μm to 117 μm across the sample.

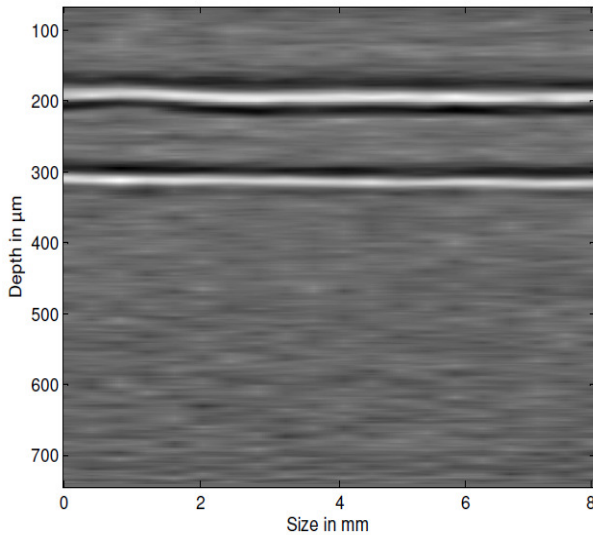


Figure 3: Time-domain THz tomography - 2D cross-section through a two layered (coated) solid dosage form. The first horizontal line indicated the air to coating interface. And the second horizontal line indicates the coating to body interface. The mean thickness of the coating is 100 μm .

IV. TIME-DOMAIN TERAHERTZ SPECTROSCOPY

Time-domain terahertz imaging can do even more than tomography. It is also possible to analyze the chemical composition of tablets. Therefore, the time domain signal has to be time-partitioned Fourier transformed. In the frequency domain it is possible to analyze the chemical composition of the tablet according to their absorption characteristics and display two- or three-dimensional concentration maps. Time-domain spectroscopy is mainly done in transmission mode because of the higher interaction of the terahertz pulse with the sample. In reflection mode this is a challenging task because terahertz radiation penetrates only to a certain depth and thus interacts only with part of the sample. However, a lot of substances used in tablets show significant absorption features in their terahertz spectra. As an example the two-dimensional distribution of glutamic acid is shown in Fig. 7. It is visible that the distribution of the analyzed substance has low variations in the center of the tablet but at the edges the variations are getting significantly higher.

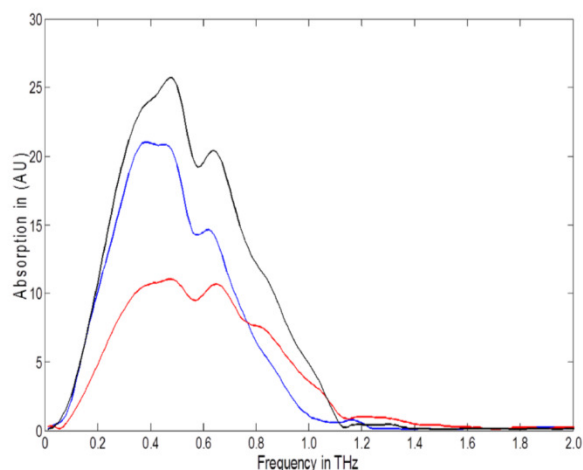


Figure 5: Time-domain THz spectroscopy – absorption spectra of three different chemical components (L-tryptophan, L-lysine, BSA).

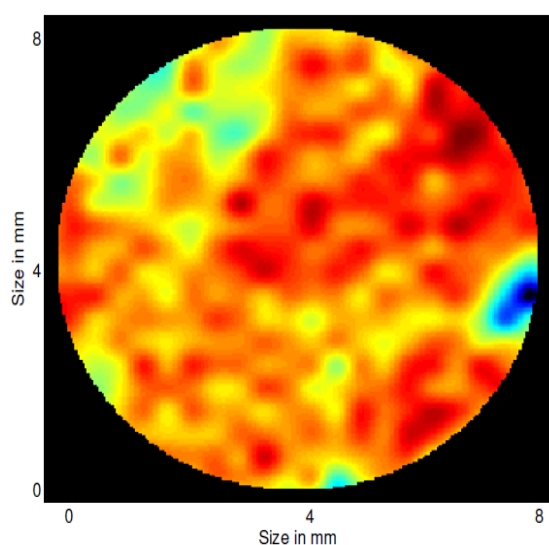


Figure 6: Time-domain THz spectroscopy - two-dimensional distribution of L-glutamic acid across the sample. The sample shows low variations in the center of the tablet but at the edges the variations are getting significantly higher.

V. CONCLUSIONS

Preliminary results indicate that terahertz imaging spectroscopy can be used to investigate the geometrical structure of solid dosage forms. It is possible to detect structural defects like delaminations, inclusions, and the presence or absence of inner structures. Moreover, the chemical composition and distribution of the chemical components of solid dosage forms can be analyzed. Tablets have a fingerprint that is unique to the coating, the contents, and potentially the manufacturer. These fingerprints are sensitive to small variances in a product, and every tablet manufactured has a fingerprint that is specific to its physical

structure and chemical composition. This fingerprint can be used for quality control or for the detection of counterfeit drugs. However, there still remain several challenges in the application of THz measurement equipment for in-line measurements. The non-flat shape of solid dosage forms is one of the challenges which can be addressed with shape-specific optics and handling systems. Future work includes the analysis of a greater variety of prescription drugs.

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