Analysis of Coating Structures and Interfaces in Solid Oral Dosage Forms by Three Dimensional Terahertz Pulsed Imaging

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Received 26 May 2006; accepted 29 August 2006

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20789

ABSTRACT: Three dimensional terahertz pulsed imaging (TPI) was evaluated as a novel tool for the nondestructive characterization of different solid oral dosage forms. The time-domain reflection signal of coherent pulsed light in the far infrared was used to investigate film-coated tablets, sugar-coated tablets, multilayered controlled release tablets, and soft gelatin capsules. It is possible to determine the spatial and statistical distribution of coating thickness in single and multiple coated products using 3D TPI. The measurements are nondestructive even for layers buried underneath other coating structures. The internal structure of coating materials can be analyzed. As the terahertz signal penetrates up to 3 mm into the dosage form interfaces between layers in multilayered tablets can be investigated. In soft gelatin capsules it is possible to measure the thickness of the gelatin layer and to characterize the seal between the gelatin layers for quality control. TPI is a unique approach for the nondestructive characterization and quality control of solid dosage forms. The measurements are fast and fully automated with the potential for much wider application of the technique in the process analytical technology scheme. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:330–340, 2007

Keywords: terahertz pulsed imaging; far infrared; structural imaging; coating analysis; film coating; sugar coating; tablets; multilayer tablet; soft gelatin capsules; process analytical technology (PAT)

INTRODUCTION

In the development of solid oral dosage forms a trend towards the development of more sophisticated coatings or layered structures to alter the release kinetics of the active pharmaceutical ingredient (API) can be observed.[1,2] With the advent of more complex processes for the production of these structures and the demand for a rigorous process understanding by the regulatory bodies an exact characterization and control of these processes and the resulting dosage form properties becomes essential for the pharmaceutical industry. However, to date most of the methods to analyze coating properties are unspecific (e.g., weight gain during coating) or destructive to the sample (e.g., electron microscopy or infrared imaging of cross sections through a tablet).[3–6]

Recently, terahertz radiation has been used in pharmaceutical analysis predominantly in spectroscopy for the study of solid state properties such as polymorphism,[7,8] phase transitions,[9,10]

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Journal of Pharmaceutical Sciences, Vol. 96, 330–340 (2007)

and hydrate forms.[11] The interactions of terahertz radiation with organic molecular crystals have been studied and first interpretations of the spectral features have been made.[12,13] It was observed that crystalline materials generally exhibit strong absorption features in this frequency range whereas predominantly amorphous materials, such as many pharmaceutical excipients are semitransparent to terahertz radiation. This enables a reasonable penetration of the terahertz pulse into the sample specimen which in turn allows the three dimensional spatial resolution of interfaces within the sample. A first review on the field was published recently.[14]

In an earlier work we have demonstrated how terahertz pulsed imaging (TPI), using pulsed coherent light in the far infrared region of the electromagnetic spectrum, can be used for the nondestructive analysis of coated tablets.[15] In that study the sample was kept stationary and pulses of terahertz radiation were focused onto the tablet. The surface was scanned with the terahertz beam. Using this approach the sample area is quite restricted due to size and curvature of a typical biconvex pharmaceutical tablet. Additionally the sample would have to be turned manually in order to examine both faces of a tablet. To overcome this limitation we have developed a robotic system for the fully automated scan of a typical pharmaceutical solid dosage form.

In the present study, this new setup was evaluated for its use as a novel tool for the nondestructive characterization of different solid oral dosage forms.

EXPERIMENTAL

Materials

Tablet A: Dicolfenac-ratiopharm® 50 (Ratiopharm GmbH, Germany) enteric-coated tablets containing 50 mg diclofenac, coating material based on 1:1 copolymer of 2-methacrylic acid and ethyl acrylate (batch #1 12 tablets, batch #2 30 tablets). Tablet B: Sinupret® forte Dragees (Bionorica, Germany) sugar-coated tablets containing a mixture of different herbal drugs. Tablet C: Diclofenac-ratiopharm® uno (Ratiopharm GmbH, Germany) multilayered controlled release tablets based on the Geomatrix® quick slow release technology.[16] Capsule A: Spalt liqua (Whitehall-Much GmbH, Germany) softcaps containing 200 mg ibuprofen in a liquid formulation. All sample tablets originated from the same production batch if not stated otherwise.

Three Dimensional Terahertz Pulsed Imaging

In this study, the solid dosage forms were analyzed using a TPI imaga2000 system (TeraView, Cambridge, UK). The generation of terahertz radiation in this system is based on a photoconductive switch setup as described previously.[15] It is adapted to meet the specific needs of this application. Terahertz photoconductive emitters rely on the production of few-cycle terahertz pulses using an ultrafast (femtosecond) laser to excite a biased photoconductive antenna. This technique is inherently broadband, with the emitted power distributed over several THz (typically 60 GHz–3 THz, corresponding to 2–100 cm^{-1}). Pulsed terahertz emission in photoconductive antennas is produced when the current density, j, of a biased semiconductor is modulated on subpicosecond timescales $E_{THz} \propto dj/dt$.[17] The change in current density mainly arises from the acceleration of photogenerated carriers under an external electric field. Coherent detection of the incident THz radiation can be performed in a similar photoconductive antenna circuit.[18] By gating the photoconductive gap with a femtosecond pulse synchronized to the terahertz pulse, a dc signal that is proportional to the terahertz electric field may be measured. Hence, both the amplitude and phase of the incident THz wave can be obtained. Further, by varying the optical path length to the receiver, the entire terahertz time-domain can be sampled. The ability to measure the electric field of the signal in this setup is in contrast to the signal detection employed in most other spectroscopic techniques where only the signal intensity is recorded. The resulting terahertz waveform therefore exhibits positive as well as negative signal.

In this particular system (see Fig. 1), the beam from the ultrafast femtosecond laser is split into two components, a pump beam and probe beam, with one used to illuminate the emitter and receiver respectively. A rapid scanning delay line, is then incorporated into the probe beam to vary the difference in optical delay around zero between the incoming terahertz pulse and the probe laser pulse at the detector, thus allowing both the delay position and the lock-in output of the modulated external electrical field to be digitized and reinterpolated to obtain the terahertz field as a function of optical delay in real time. The two laser beams are