Critical Factors in the Measurement of Tablet Film Coatings Using Terahertz Pulsed Imaging

DANIELA BROCK,[1] J. AXEL ZEITLER,[2] ADRIAN FUNKE,[3] KLAUS KNOP,[1] PETER KLEINEBUDDE[1]

[1]Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Düsseldorf 40225, Germany

[2]Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge CB2 3RA, UK

[3]Global Chemical and Pharmaceutical Development, Bayer Pharma AG, Berlin 13353, Germany

Received 16 January 2013; revised 21 February 2013; accepted 5 March 2013

Published online 5 April 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23521

ABSTRACT: The present work gives an insight into some key measurement and signal processing considerations in terahertz pulsed imaging (TPI). TPI is increasingly used for the measurement of the spatial variation of coating thickness on coated solid dosage forms. The potential of TPI for the assessment of coating thickness distributions and the use in process development is described in recent literature. However, some critical factors need to be taken into account when working with this technique. These are (1) the signal processing of the raw data, (2) the influence of the composition of the sample matrix on the TPI signals and subsequent coating analysis, (3) signal distortions that can occur at tablet edges or areas with defects, and (4) the refractive index as a key parameter in the quantification of layer thickness. In this paper, we will highlight to what extent these factors impact on the qualitative and quantitative analysis of TPI data and how artifacts and misinterpretation of data can be avoided to ensure fully quantitative and robust measurements. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:1813–1824, 2013

Keywords: terahertz pulsed imaging; active coating; deconvolution; absorption coefficient; coating thickness; refractive index; imaging methods; crystallinity; osmotic pumps; solid dosage form

INTRODUCTION

In recent years, terahertz pulsed imaging (TPI) has been systematically evaluated as a technique for nondestructive three-dimensional imaging of pharmaceutical solid dosage forms. When imaging tablets, it was found that TPI can provide information on the spatial variation of coating thickness over the tablet surface for both, external and buried layers. Furthermore, the physical properties of the investigated dosage form such as coating density and surface roughness can be investigated. Detailed information on the technique is provided by Zeitler et al.[1] and Shen and Taday.[2]

To date, the most promising results were demonstrated in the measurement of film coating thickness. Ho et al.[3,4] showed how TPI can be used to identify defects in the coating structure and to quantify the spatial variability of coating thickness over the entire tablet surface. With their measurements, the authors were able to reveal areas on the tablet that were critical for the dissolution performance of the tablets. Furthermore, proof-of-principle studies into the applicability of the technique for coating process development[5] and its in-line applicability were reported.[6] In addition, Zeitler et al.[1] showed the potential of the technique to reveal the internal structure of more complex samples, such as sugar-coated tablets that exhibit multiple coating layers or multilayer tablets.

Apart from measuring the coating thickness, it was demonstrated that TPI can be used to assess the surface roughness and the density of the tablet coating. For sustained release film-coated tablets, it was possible to correlate these parameters with the drug release.[7] Differences between laboratory- and pilot-scale batches of a pan-coating process were identified based on this analysis.

Additional Supporting Information may be found in the online version of this article. Supporting Information

Correspondence to: Peter Kleinebudde (Telephone: +49-211-8114220; Fax: +49-211-8114251; E-mail: kleinebudde@hhu.de)

Journal of Pharmaceutical Sciences, Vol. 102, 1813–1824 (2013)

Given the increasing amount of studies and use of the technique in industry, it is important to highlight some of the key measurement and signal processing considerations in more detail to avoid artifacts and thus ensure fully quantitative and robust TPI measurements. First, the impact of the signal processing on the quantitative analysis of TPI data is discussed as it is an essential step prior to data analysis. Furthermore, effects of the sample matrix, such as crystallinity and particle size, on the TPI data and its impact on quantitative coating analysis are evaluated. The quality of TPI signals close to tablet edges and the drilling region of an active-coated gastrointestinal therapeutic system is furthermore assessed. Finally, the impact of various process conditions on the refractive index as a crucial parameter for the determination of absolute coating thickness values is investigated. The present study shall give the reader an overview of these measurement and signal processing considerations and shall help to identify some critical factors in the measurement of tablet film coatings using TPI.

MATERIALS AND METHODS

Manufacturing of the Dosage Forms

Dosage form A, biconvex placebo tablets (8 mm diameter, average weight: 200 mg), consisting of 49.5% lactose (Granulac 70; Meggle Pharma, Wasserburg, Germany), 45% microcrystalline cellulose (Avicel PH 101; FMC Biopolymer, Philadelphia, Pennsylvania, USA), 5% croscarmellose, and 0.5% magnesium stearate (wt % solids), were coated using a side-vented pan coater (BFC5; LB Bohle, Ennigerloh, Germany) at 3 kg scale.

The coating consisted of 64% Kollicoat IR (polyvinyl alcohol–polyethylene glycol graft copolymer; BASF, Ludwigshafen, Germany), 15% talc, 15% titanium dioxide, and 6% iron oxide red (wt % solids). Film coating was performed until 30% weight gain of the tablet cores was reached. Samples were withdrawn at set time intervals throughout the coating process.

A part of the batch of dosage form A was subsequently coated with a second layer, resulting in samples of dosage form B. The second coating layer consisted of 75% Walocel HM5 PA2910 (hypromellose; Wolff Cellulosics, Bomlitz, Germany) and 25% polyethylene glycol 1500 (wt % solids). Here, a total coating mass of 8.75% weight gain was applied.

Dosage form C was based on a gastrointestinal therapeutic system (GITS; Bayer Pharma AG, Leverkusen, Germany), a two-layer tablet core coated with a polymer diffusion membrane. One layer of the tablet core contained the active pharmaceutical ingredient (API) nifedipine (NIF), whereas the other half consists of an osmotic blend comprising sodium chloride (NaCl), red iron oxide, and polyethylene oxide. According to the color, the first layer of the tablet core will be referred to as the yellow tablet face whereas the other layer will be referred to as the red tablet face. The diffusion membrane of the GITS consists of celluloseacetate (CA) and polyethylene glycol 3350 (PEG). An orifice is drilled into this membrane on the yellow tablet face by laser ablation to release the API from the tablet core. The diameter of the GITS was either 9.1 mm at an average weight of 280 mg per tablet and a drug load of 30 mg NIF or 10.6 mm at an average weight of 531 mg per tablet and 60 mg NIF.

On top of the GITS, an active coating layer was applied. The coating suspension of the active layer consisted of micronized candesartan cilexetil (CAN) and Opadry II 85F clear (OPA; polyvinyl alcohol based polymer mixture; Colorcon, Dartford, UK). Coating was performed at laboratory scale (3.5–8 kg), pilot scale (37–43 kg), or production scale (250 kg) in side-vented pan coaters at varying process conditions (BFC5, BFC5/10, BFC50, and BFC400; L. B. Bohle). Detailed information on the process conditions is given in Table S1 in the supplementary data.

Terahertz Pulsed Imaging

All TPI measurements were performed using a TPI imaga 2000 system (TeraView Ltd., Cambridge, UK). Imaging was performed by mapping over the tablet surface at a resolution of $200 \times 200\,\mu m^2$. Depending on the tablet dimensions, this resulted in approximately 1500–3300 data points per tablet surface (top, center, or bottom).

Dosage Forms A and B

Tablets from coating endpoint as well as samples throughout the coating process (only dosage form A) were subdued to TPI analysis. The penetration depth was 2 and 1 mm in air for dosage forms A and B, respectively.

Dosage Form C

From each batch of samples either 10 or 36 tablets were measured at coating endpoint. The penetration depth of the THz pulse was set to 2 mm in air.

Layer thickness analysis was performed using TPIView version 3.0.3 (TeraView Ltd.). Subsequent numerical analysis was performed using Matlab (R2011b, The Mathworks, Natick, Massachusetts).

Terahertz Time-Domain Spectroscopy

Physical mixtures of the raw excipients and polyethylene (PE) were prepared by mixing 360 mg PE and 50mg sample material. The mixtures were compressed into flat-faced disks using a biplanar die of 13 mm diameter. The reference disk consisted of 360 mg PE.

Terahertz time-domain spectroscopy (THz-TDS) measurements were performed on 2–3 samples per