European Journal of Pharmaceutics and Biopharmaceutics 106 (2016) 20–25

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

The application of terahertz pulsed imaging in characterising density distribution of roll-compacted ribbons

Jianyi Zhang [a], Chunlei Pei [a], Serena Schiano [a], David Heaps [b], Chuan-Yu Wu [a,*]

[a] Department of Chemical and Process Engineering, University of Surrey, Guildford GU27XH, UK
[b] Advantest Inc., Princeton, NJ, USA

ARTICLE INFO

Article history:
Received 1 October 2015
Revised 2 January 2016
Accepted in revised form 19 January 2016
Available online 27 January 2016

Keywords:
Roll compaction
Terahertz imaging
Density distribution

ABSTRACT

Roll compaction is a commonly used dry granulation process in pharmaceutical, fine chemical and agrochemical industries for materials sensitive to heat or moisture. The ribbon density distribution plays an important role in controlling properties of granules (e.g. granule size distribution, porosity and strength). Accurate characterisation of ribbon density distribution is critical in process control and quality assurance. The terahertz imaging system has a great application potential in achieving this as the terahertz radiation has the ability to penetrate most of the pharmaceutical excipients and the refractive index reflects variations in density and chemical compositions. The aim of this study is to explore whether terahertz pulse imaging is a feasible technique for quantifying ribbon density distribution.

Ribbons were made of two grades of microcrystalline cellulose (MCC), Avicel PH102 and DG, using a roll compactor at various process conditions and the ribbon density variation was investigated using terahertz imaging and section methods. The density variations obtained from both methods were compared to explore the reliability and accuracy of the terahertz imaging system. An average refractive index is calculated from the refractive index values in the frequency range between 0.5 and 1.5 THz. It is shown that the refractive index gradually decreases from the middle of the ribbon towards to the edges. Variations of density distribution across the width of the ribbons are also obtained using both the section method and the terahertz imaging system. It is found that the terahertz imaging results are in excellent agreement with that obtained using the section method, demonstrating that terahertz imaging is a feasible and rapid tool to characterise ribbon density distributions.

1. Introduction

For fine powders made of materials sensitive to heat and moisture, roll compaction is the preferable granulation process in order to improve their process-ability and performance during handling and processing, such as flow-ability, bulk density and mixing homogeneity. In roll compaction, powders are compressed to form ribbons or flakes when they are fed into the gap between two counter rotating rolls. The ribbons and flakes are then milled into granules. The granule properties (such as size and size distribution) are determined by density distributions of ribbons. Therefore it is crucial to characterise the ribbon density distribution for the purpose of process control and process optimisation. In particular, a robust in-line or on-line approach is urgently needed. Various methods were developed recently to determine ribbon density distribution [1,2], including the section method, micro-indentation and X-ray computed tomography. These studies showed that the density distributions of roll-compacted ribbons were not uniform and depended upon the roll compactors used and the process conditions. For example, for ribbons produced using a roll compactor with fixed cheek plates, the density in the regions close to the ribbon edges was generally lower than that in the centre. Although these methods can be used to determine ribbon density distribution accurately, they involve tedious experimental procedure and are not suitable for online or inline measurements. There is hence an urgent demand to develop an effective method that can measure the density distribution of roll-compacted ribbons accurately and rapidly.

Terahertz pulsed imaging (TPI) uses terahertz radiation that consists of electromagnetic waves with frequencies between infrared and microwave region (300 GHz–10 THz) and wavelengths ranging from 1 mm to 0.1 mm. This broad bandwidth gives terahertz radiation the ability to penetrate a wide variety of non-conducting materials, including most of pharmaceutical excipients [3]. In addition, the radiation in the terahertz region has a low

* Corresponding author. Tel.: +44 1483 683506.
E-mail address: C.Y.Wu@surrey.ac.uk (C.-Y. Wu).

http://dx.doi.org/10.1016/j.ejpb.2016.01.012
0939-6411/

photon ionising energy, making the terahertz radiation a safe and attractive method for analysing pharmaceutical products in manufacturing processes [4]. It has hence attracted increasing interest with potential applications in characterising chemical and physical properties of particulate materials.

TPI systems can be operated in two different modes: transmission and reflection. For the transmission mode, the terahertz emitter (transmitter) and detector were positioned at the opposite sides of the sample. As the incident terahertz hit the sample, part of it was absorbed by the samples and part of radiation travelled through the sample. The penetrated terahertz beam continued to travel and was received by the detector. The system recorded the time-of-flight of the terahertz pulse travelling through the sample [5]. For the reflective mode, when the terahertz pulse travelled into the sample, the reflection of radiation always occurred as long as the material property changed along its travel path, such as at the surface of the sample, or at the interface of the multilayer tablets. The reflected pulses were detected and the time-domain waveforms of the pulses were recorded using time-resolved detection [6].

Using the reflective TPI, layer thickness, such as coating thickness, could be determined. For example, Zeitler et al. [4] examined many commercial pharmaceutical dosage forms such as film-coated tablets and capsules and constructed thickness maps for all the samples. Ho et al. [7] compared coating thickness determined using TPI with the optical microscopic measurements and explored the reliability of TPI systems on coating thickness measurement. An excellent agreement was obtained, demonstrating the accuracy of TPI. Spencer et al. [8] explored the advantage of the TPI system as a non-destructive method to qualify sustained-release tablets, in which all the tablets were mapped using a TPI system to identify the coating thickness inhomogeneity before the dissolution tests. An empirical relationship between the mean coating thickness and mean dissolution time was obtained. In addition, the coating thickness distribution can also provide vital information on potential tablet defects to improve production performance [9].

Moreover, as shown by Palermo et al. [10], the TPI could also be used to determine densities of solid oral dosage forms. Because the terahertz radiation was mainly attenuated by absorption, the terahertz images revealed spectral characters of tablets as the absorption intensity was directly related to the density and the chemical composition of the material. Pore et al. [11] explored the impacts of the tablet density on the reflective index values. It was shown that the reflective index increased as the tablet density increased. May et al. [12] examined tablet surface hardness using TPI and showed that there is a strong correlation between the reflective index and the tablet crushing force for flat-surfaced and biconvex tablets. Furthermore, TPI was also used to examine chemical composition of the dosage forms [13], for which the terahertz reflection signal from a mirror was treated as the reference and the unique characteristics of the sample were extracted by comparing the signal from sample reflection (terahertz radiation after sample reflection and absorption) with the reference signal. Shen et al. [13] also successfully mapped the chemical distribution of lactose and sucrose over the tablet surface.

Although a wide range of application using TPI have been reported in the literature, its application in ribbon density mapping is still in its infancy. A preliminary study reported by Sullivan et al. [14] illustrated the feasibility of TPI in determining density distributions of roll-compacted ribbons. The purpose of this paper is to further explore the potential of this technique in quantifying density distributions of pharmaceutical ribbons, for which ribbons produced using different material properties at various process conditions were examined using TPI and the section method [1], and the obtained density distributions are compared to assess the accuracy of TPI.

2. Materials and methods

Microcrystalline cellulose (MCC) of two different grades, Avicel PH 102 (Fig. 1a) and DG (see Fig. 1b) (FMC, Biopolymer, USA) were used as the model materials. MCC Avicel PH102 is a widely used pharmaceutical excipient while MCC DG is a newly formulated microcrystalline-based excipient composed of 75% of MCC and 25% of anhydrous calcium phosphate. SEM (scanning electron microscopy) images of these powders are shown in Fig. 1.

In order to establish a correlation between the measured reflective index using the TPI technique with the bulk density, the powders were compressed in a die of 13 mm in diameter under various compression pressures so that tablets of different thickness and relative densities but same mass (i.e. 350 mg) were produced, as illustrated in Fig. 2a. Furthermore, the powders were also compressed using a custom-made roll compactor [1] at different roll speeds (1–5 rpm) and different roll gaps (0.8–1 mm) so that how roll speed and roll gap affect the density distribution could be explored. The roll compactor has two smooth rolls of 200 mm in diameter and 46 mm in width. The density distribution of produced ribbons (Fig. 2b) were first determined using the section method, as used in Miguelez-Moran et al. [1]. In this method, ribbons were cut into small pieces using a bandsaw, and the mass and volume of each piece were determined from the measurements

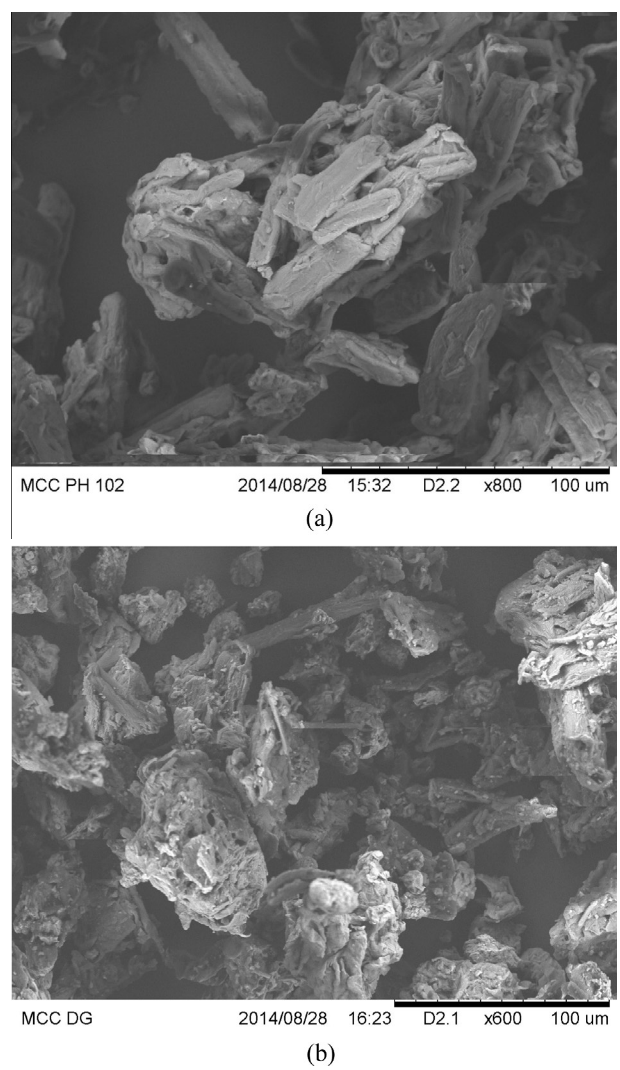

Fig. 1. SEM images of (a) MCC PH102 and (b) MCC DG.