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Research paper

Terahertz pulsed imaging as an analytical tool for sustained-release tablet film coating

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ABSTRACT

The ability of terahertz pulsed imaging (TPI) to be employed as an analytical tool for monitoring a film coating unit operation and to assess the success of a subsequent process scale-up was explored in this study. As part of a process scale-up development, a total of 190 sustained-release tablets were sampled at 10% increments of the amount of polymer applied, from a lab-scale and a pilot-scale coating run. These tablets were subjected to TPI analysis, followed by dissolution testing. Information on tablet film coating layer thickness and variations in coating density were extracted using TPI. It was found that both terahertz parameters were more sensitive and informative to product quality when compared with measuring the amount of polymer applied. For monitoring the film coating unit operation, coating layer thickness showed a strong influence on the dissolution behaviour for both the lab-scale and the pilot-scale batches. An R^2 of 0.89, root mean square error (RMSE) = 0.22 h (MDT range = 3.21–5.48 h) and an R^2 of 0.92, RMSE = 0.23 h (MDT range = 5.43–8.12 h) were derived from the lab-scale and pilot-scale, respectively. The scale-up process led to significant changes in MDT between the lab-scale and pilot-scale. These changes in MDT could be explained by the differences observed in the film coating density on samples with similar amount of polymer applied between the lab and the pilot-scale. Overall, TPI demonstrated potential to be employed as an analytical tool to help refine the coating unit operation and the scale-up procedure.

1. Introduction

Tablet film coating is a pharmaceutical unit operation modifying simple compressed tablets. Tablets are coated to improve their aesthetic appeal, to mask an odour, to disguise the taste, to improve drug stability, or most importantly to achieve a modified drug release profile [1]. Slight changes in the coating equipment and coating parameters may cause variations in the physicochemical properties of the film and may consequently compromise the coating quality [2]. Coating defects like twinning, cratering and blistering are visible to the naked eye and generally can be picked up by the operator [3]. On the other hand, variations in the film coating thickness and density cannot easily be detected without the help of a process analytical tool (PAT). Monitoring and controlling coating quality is thus important to prevent output risks including batch reprocessing, batch reject and product recall [2]. Being able to accurately determine coating quality is of paramount significance for a better understanding and appropriate control of the coating process in order to improve manufacturing efficiency and to avoid scale-up delays [4].

Traditionally, weight gain and the amount of coating polymer applied are monitored to determine tablet film coating quality. These parameters are inherently non-specific and often fail to predict the performance of the dosage form in subsequent dissolution testing [5]. Dissolution and bioavailability testing are currently the bench-mark for assessing the success of a scale-up operation in the film coating process [2]. Numerous techniques have been used to study the different aspects of film coating quality, including light and electron-microscopy, magnetic resonance imaging (MRI), near infrared (NIR) spectroscopy, Raman spectroscopy, and laser

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induced break-down spectroscopy [6–15]. Unfortunately, to determine the coating layer thickness these techniques are often destructive, have no capability to resolve multiple coating layers with a single-point measurement or may require the set-up and maintenance of robust multivariate analysis models for data interpretation.

Terahertz radiation resides in the far-infrared region of the electromagnetic spectrum (2–120 cm^{-1}). With longer wavelength than NIR, terahertz radiation can penetrate most pharmaceutical excipients with a penetration depth of around 3 mm (depending on the refractive index of the material), thus allowing the non-destructive analysis of most solid dosage forms [16,17]. For coating quality analysis, coating layer thickness and film coating density can be directly determined without recourse to sophisticated multivariate analytical models. These two coating quality parameters are important for the subsequent dissolution performance of a particular film coated dosage form [18,19].

The terahertz pulsed imaging (TPI) has been used to discriminate between an innovator and a generic product by clearly mapping out the coating features of the sugar coat of the two products. Using a single-point measurement the authors concluded that the sugar coating on the innovator product is far more complex than that of the generic product [20]. The detailed set-up for the TPI instrument and the analysis of various solid dosage forms using TPI had been previously described [21], and its capabilities to construct 2D maps and 3D models of film coating defects and to determine coating uniformity has been demonstrated [22]. TPI has also been validated by microscopic imaging with respect to the accuracy of measuring coating layer thickness [22]. A new terahertz parameter (terahertz electric field peak strength/TEFPS) was introduced, and has demonstrated potential alongside coating layer thickness determination to extract information on the density of the tablet film coating [18].

In this study, we investigate how both terahertz parameters (coating layer thickness and TEFPS) can be applied to monitor coating quality. Moreover we assess the success of a film coating scale-up procedure using these terahertz parameters.

2. Materials and methods

2.1. Sustained-release tablets

Both lab and pilot-scale batches of tablet cores were coated with the same film coating formulation. Tablet cores were biconvex (3 mm in height, 8 mm in diameter and an average weight of 252 mg), and contained 10% w/w diprophyllin (API), 84.5% w/w lactose monohydrate (Flowlac®), 5% w/w vinylpyrrolidone–vinyl acetate copolymer (Kollidon® VA 64) and 0.5% w/w magnesium stearate. The coating formulation used was as follows: 50% w/w polyvinyl acetate (Kollicoat® SR 30 D), 6% w/w polyvinyl alcohol–polyethyleneglycol graft copolymer (Kollicoat® IR), 0.075% w/w polyoxyethylene (20) sorbitan monooleate (Polysorbat 80), 0.3% w/w glycerolmonostearate, 0.75% w/w triethylcitrate and 42.87% w/w deionised water.

2.2. Coating process (lab-scale)

The lab-scale batch was coated using a BFC5, Bohle Film Coater (L.B. Bohle, Ennigerloh, Germany). The dimensions for the BFC5 coating pan are 316 mm in diameter and 356 mm in pan length, accommodating a 4 kg batch size. A single two-way spray nozzle (type 970/7-1 S75, Düsen-Schlick GmbH, Untersiemau, Germany) was used to apply the coating solution for the lab-scale batch. Ten samples were randomly selected during the coating process, at 10% increments of the amount of sustained-release polymer applied (1.7, 3.7, 5.2, 7.0, 8.7, 10.5, 12.2, 14.0, 15.7 and 17.5 mg/cm^2).

2.3. Process scale-up, coating process (pilot-scale)

A BFC25, Bohle Film Coater (L.B. Bohle, Ennigerloh, Germany) was used to coat the pilot batch (batch size 20 kg). The coating pan dimensions are 546 mm in diameter and 630 mm in length. The coating process was carried out in the same manner as for the lab batch with similar coating parameters (slight changes were necessary to accommodate the increased batch size). Five of the two-way spray nozzles (type 970/7-1 S75) were used (Düsen-Schlick GmbH, Untersiemau, Germany) to spray coat the tablets. Random selection of ten tablets was carried out after the following amounts of sustained-release polymer were applied: 1.8, 3.6, 5.5, 7.3, 9.1, 10.9, 12.7, 14.5 and 18.2 mg/cm^2. All sampled tablets were stored and measured under the same ambient conditions.

2.4. TPI analysis

The imaging process was performed with a TPI Imaga2000 (TeraView, Cambridge, UK), using the same data acquisition process previously detailed [22]. Briefly, ultra-short bursts of coherent broadband terahertz radiation were generated and detected with photoconductive semiconductor devices. Using time-of-flight measurements, the imaging process can either be single-point (measurement time approximately 50 ms) or a whole surface scan (a series of singe-point measurements) over the entire solid dosage form. For the tablets examined in this study, the current image acquisition time for a whole surface scan (top and bottom surfaces and the central band of the coated tablet) was around 45 min. The instrument was used in an off-line mode in this study. Due to the transparent or semi-transparent nature of most pharmaceutical excipients in the terahertz region of the electromagnetic spectrum, the incident terahertz radiation is able to travel through the entire film coating. A portion of the radiation is reflected back at each tablet interface due to changes in the refractive indices, resulting in a time-domain terahertz electric field signal. This time-domain signal is the basis for the construction of 2D terahertz surface maps and 3D tablet models, and can be visualised as a cross-sectional image that looks similar to an ultrasound B-scan (Fig. 1).

Both terahertz parameters (coating thickness and TEFPS) were generated from an average of 1200 pixels around the central band of the tablet. The central band was chosen as it is the weakest area of a sustained-release tablet and is rate governing during dissolution [23]. The exact calculations of these parameters were explained in Ho et al. [18,22]. The TEFPS is expressed as a percentage value (%), and was derived from the surface reflection of the sample over the peak intensity of the incident pulse, measured from the reflection off a reference mirror. From the temporal terahertz waveform, using the peak-to-peak or peak-to-trough distance (the direction of the peak is dependent on the change of the refractive index at the tablet coating/core interface) the coating layer thickness (d_{coat}) at each pixel can be determined, using the relationship: $2d_{coat} = \Delta t\ c/n$, where Δt is the time delay between the terahertz reflections, c is the speed of light and n is the refractive index of the coating matrix. Terahertz refractive indices of 1.68 and 1.79 were measured using the spectroscopy set-up in transmission mode and subsequently employed for calculating the film coating layer thickness of the lab and pilot-scale tablets, respectively.

2.5. Dissolution testing

Dissolution testing was carried out on the same tablets that were used for TPI analysis and was performed in accordance with the USP guidelines for sustained-release dosage forms. A USP 2 – paddle dissolution apparatus was used. About 900 ml of water