Evaluating critical film coating characteristics of sustained-release coated pellets with different size using terahertz pulsed imaging

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Abstract: In this study different sized sustained-release coated pellets (6, 2.5 and 1 mm in diameter) were investigated using terahertz pulsed imaging (TPI). Ten pellets from each batch of metoprolol succinate layered sugar starter cores coated with a 75:25 (w/w) polymer blend of Kollicoat SR and Kollicoat IR (approximate coating thickness of 60 µm, according to the weight gain) were mapped individually to evaluate the effect of size on coating thickness and morphology (depicted by the terahertz electric field peak strength, TEFPS). The TPI measurements were carried out on a pellet surface area of approximately 33, 2.2 and 0.4 mm^2 for pellets with 6, 2.5 and 1 mm diameters, respectively, and the interface between polymer coating/drug layer and drug layer/sugar core was successfully determined. Results indicated a large variation in the mean coating thickness (CT) between all pellets sizes. Smaller pellets showed a higher mean CT of 70 µm (1 mm) and 81 µm (2.5 mm) compared to 6 mm pellets (50 µm), suggesting a better coating efficiency for smaller pellets. With no differences in surface morphology observed using scanning electron microscopy (SEM), differences in the mean TEFPS values between 6 mm pellets (17.6%) and 2.5/1 mm pellets (2.2 and 2.6%, respectively) were related to signal distortion due to the increase in curvature of smaller pellets. Although the largest pellets showed the thinnest CT, the fastest drug release was obtained from the smallest pellets due to the larger surface area exposed to

the dissolution media. TPI proved highly suitable to evaluate film coating characteristics as well as to detect the drug layer/core interface of different sized sustained-release pellets.

Keywords: Terahertz pulsed imaging (TPI); image analysis; controlled release, coating; unit operations; pellets; dissolution.

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1. Introduction

Sustained release film coating of multiparticulate systems is commonly performed to achieve modified drug release behaviour[1]. However, the desired drug release over a prolonged time period quite often directly correlates with the final film coating quality, including the coating thickness and uniformity[2]. Routinely, indirect monitoring methods such as the product weight-gain and the amount of coating polymer applied are used to express the film coating thickness and quality of coated multiparticulate systems. Often these non-specific parameters do not give reliable information on the coating characteristics. For pellets consisting of drug-layered sugar starter cores coated with sustained-release coating formulations and different sizes, the non-specific character of weight gain measurements as a sole indicator of the coating quality, may be insufficient. Other more specific techniques that have been employed to analyse the coating quality of coated pellets include nuclear magnetic resonance spectroscopy (NMR), energy dispersive X-ray imaging (EDX) and confocal laser scanning microscopy (CLSM)[3,4,5].

Another more recently established non-destructive technique to gain deeper understanding on film coating characteristics (including coating thickness and uniformity) is terahertz pulsed imaging (TPI). Terahertz radiation is part of the far infrared region of the electromagnetic spectrum (2 cm^{-1} and 120 cm^{-1}) and most of the well-established polymer formulations used in film coatings are transparent or semitransparent to the pulsed coherent light used in TPI[6]. Hence, the generated terahertz pulse can penetrate through the sample and the partial reflection caused by interfaces within the sample structure can be measured against time. Thus, single or multiple layer thicknesses can be derived from the peak-to-peak distance in the time-domain signal (time delay of the terahertz pulse). Not only parameters like coating thickness (CT) but also coating surface roughness (depicted by the terahertz electric field peak strength, TEFPS) can be accessed by TPI[7,8]. CT and TEFPS are directly derived from the terahertz waveform and have been shown to be indicative of the subsequent dissolution behaviour of coated tablets and pellets[7,9].

In this study, TPI was used to analyse the film coating thickness and surface morphology of sustained release coated pellets of different size, in an attempt to investigate the effect of the pellets' size (6, 2.5 and 1 mm in diameter) on coating characteristics and associated drug release behaviour. Furthermore, the ability of TPI to detect both interfaces (polymer coating/drug layer and drug-layer/sugar core) was explored.

2. Experimental Section

2.1 Materials

The following materials were used: metoprolol succinate (Salutas Pharma GMBH, Germany); nonpareil sugar starter cores (diameter 710-850 µm, NP Pharma SR, France); polyvinyl acetate (Kollicoat SR 30 D; BASF, Germany), poly(vinyl alcohol)-poly(ethylene glycol graft copolymer (Kollicoat IR; BASF, Germany); hydroxypropyl methylcellulose (HPMC, Methocel E5; Colorcon, United Kingdom); triethyl citrate (TEC; Morflex, USA); talc (Luzenca Val Chisone, Italy).

2.2 Preparation of the Pellets

Preparation of the pellets was carried out by layering an aqueous drug-binder solution onto sugar starter cores of three different sizes (diameter = 3.9 mm, 1.4-1.7 mm and 710-850 µm; Boire, Lyon, France). Sugar starter cores with 3.9 and 1.4-1.7 mm diameter were layered with a suspension of metoprolol succinate (14% (w/w)) in an aqueous sucrose solution (46 % (w/w)) in a drum coater using a spray nozzle of 0.8 mm diameter and a pressure of 0.5 bar until a drug load of 10% was reached, whilst startercores with 710-850 µm diameter were layered with an aqueous drug-binder solution (20% metoprolol succinate, 1% HPMC) using a fluidized bed coater equipped with a Wurster insert (Strea 1; Aeromatic-Fielder, Switzerland) using a spray rate of 2-3 g/min, a spray nozzle of 1.2 mm diameter and an atomization pressure of 1.2 bar. The inlet temperature was 40 ± 2 °C and the product temperature 38 ± 2 °C. The method used to apply the drug layer onto the two larger sugar starter cores (3.9 and 1.4-1.7 mm in diameter) resulted in a coarse surface morphology of the pellets. Smooth pellets were obtained by spheronization of the coarse pellets for 180 s at 750 rpm prior to the application of the final film coating.

Kollicoat® IR (polyvinyl alcohol-polyethylene glycol graft copolymer) was dissolved in purified water and blended with plasticized Kollicoat® SR 30 D (an aqueous polyvinyl acetate dispersion) (overnight stirring with 5 % triethyl citrate; w/w based on the polymer content) 30 min prior to the coating process. The polymer:polymer blend ratio was 75:25 (w/w referring to the dry mass). 1.5 % of talcum was added (w/w; based on the total solids content) and the dispersion was gently stirred throughout the coating process. The process parameters were as follows: inlet temperature 38 ± 2 °C, product temperature 35 ± 2 °C, spray rate 2-3 g/min, atomization pressure 1.2 bar, nozzle diameter 1.2 mm. After coating, the pellets were further fluidized for 10 min and subsequently cured in an oven for 24 h at 60 °C. The metoprolol succinate loaded cores were coated until a coating thickness of approximately 60 µm (estimated based on weight-gain) was achieved. The final pellets had a mean diameter of 6, 2.5 and 1 mm, respectively.

2.3 Terahertz Pulsed Imaging (TPI)

A total of ten pellets of each batch was imaged individually using a TPI Imaga2000 for the large pellets (6 mm in diameter) and a TPS Spectra3000 (TeraView Ltd, Cambridge, UK) in reflection mode for the small pellets (2.5 and 1 mm in diameter). The instrument set-up for the TPI Imaga2000 was as follows: mapping step-size (point-to-point mode) = 0.1 mm; axial penetration depth in air = 2.5 mm. The instrument set-up for the TPI Spectra3000 was as follows: mapping step-size (point-to-point mode) = 0.05 mm; axial penetration depth in air = 1.5 mm. The resulting depth resolution limit with this analytical technique lies between 30-40 μm and the spatial resolution is 200 μm. Data analysis was carried out using TPIView TVL imaging software version 3.0.3. The refractive index of the coating material used to determine the accurate CT was 1.5[8] and the refractive index of the drug layer was found to be 1.81 (determined using terahertz pulsed spectroscopy in transmission mode). The TPI parameters, coating thickness (CT) and TEFPS (indicative of coating surface roughness and expressed in % of the initial signal that is reflected off the coating surface), were determined, and the drug layer thickness evaluated.

2.4 Dissolution Testing

Drug release measurements were carried out after TPI investigation of the same pellets. Pellets with the size of 6 and 2.5 mm were placed individually in an USP 32 paddle apparatus vials (Sotax, AT 7, Basel, Switzerland) filled with 900 ml and 200 ml of phosphate buffer pH 7.4 (USP 32), respectively. A paddle speed of 100 rpm and a temperature of 37°C ± 0.5°C were used for drug release testing. Detection of drug concentration in the dissolution media was carried out by using an UV/VIS spectrophotometer (Beckman DU 650, Beckman Coulter, Villepinte, France) at a detection wavelength of 222 nm. Samples were taken after predetermined time intervals (0, 0.25, 0.5, 0.75, 1, 1.5 and 2 h followed by an hourly interval up to 8 h thereafter). Pellets with 1 mm in diameter were placed individually into 2 mL Eppendorf-tubes filled with 1.5 mL phosphate buffer pH 7.4 for 8 h. The tubes were agitated in a horizontal shaker (80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Germany). At pre-determined time points (0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 h) the medium was completely removed and analyzed using a UV-visible spectrophotometer (UV-1650, Shimadzu, France) at a detection wavelength of 222 nm. The average drug release of ten pellets was calculated and the model independent similarity factor (f_2) was used to compare the dissolution performance for all pellet sizes.

3. Results and Discussion

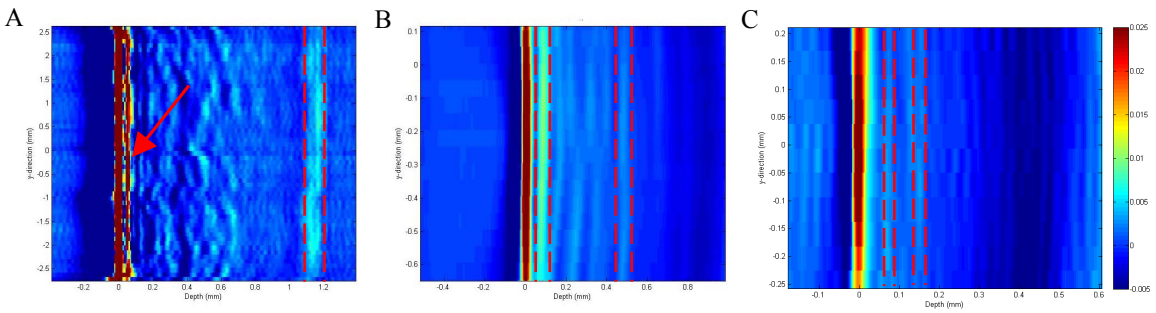
Using TPI mapping, the mean film coating thickness (CT), drug layer thickness, and the TEFPS were determined for ten sustained-release coated pellets from each batch (Table 1). The TPI investigations were carried out on a pellet surface area of approximately 33 mm^2 for the large pellets (6 mm in diameter), and 2.2 mm^2 and 0.4 mm^2 for the smaller pellets (2.5 and 1 mm in diameter).

Table 1. TPI measurements on TEFPS, coating thickness and drug layer thickness of 10 pellets from each batch.

Batch	TEFPS (%)	Coating thickness (µm)	Drug layer thickness (µm)
6 mm	17.6 ± 0.8	50 ± 1	881 ± 44
2.5 mm	2.2 ± 0.2	81 ± 2	277 ± 10
1 mm	2.6 ± 0.3	70 ± 2	95 ± 1

The interface between polymer coating layer and drug layer as well as between drug layer and sugar core could be detected in the TPI waveform and visualised in the corresponding virtual cross-sectional image (B-scan) for all pellets (Figure 1). The big red band located at 0 mm depth corresponds to the air/coating interface followed by the next band (red/yellow/light blue) representing the polymer coating/drug layer interface and a light blue band for the drug layer/sugar core interface in the cross-sectional images. Pellets with 6 mm in diameter showed a mean drug layer thickness of 881 µm ± 44 µm, whereas the mean drug layer thickness of the pellets with a 2.5 mm in diameter was found to be 277 µm ± 10 µm and 95 µm ± 1 µm for 1 mm in diameter pellets (Table I).

Figure 1. Cross-sectional images in the depth direction (terahertz B-scan) of a pellet with 6 mm (A), 2.5 mm (B) and 1 mm (C) in diameter. The red band in the images represents the air/coating interface followed by a red (indicated by a red arrow), or yellow/light blue band (indicated by red dotted lines) for the polymer coating/drug layer interface, respectively, and a light blue band for the drug layer/sugar core interface (indicated by red dotted lines). The images are projected in a plane for clarification. The colour bar shows the height of the terahertz signal [a.u.].

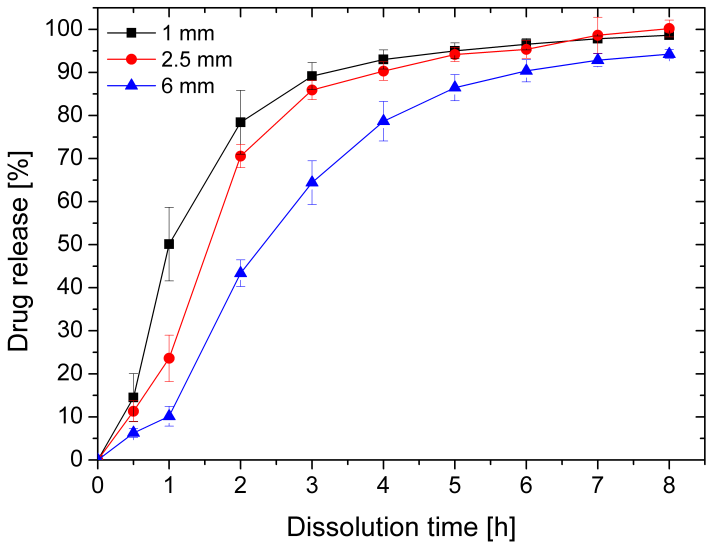


The results from the corresponding TPI maps suggested that the mean CT of the smaller pellets (81 µm for 2.5 mm in diameter pellets and 70 µm for 1 mm in diameter pellets) was higher than that of the 6 mm in diameter pellets (50 µm). This was also confirmed by scanning electron microscopy (SEM) imaging (data not shown). Although all coating processes were carried out to obtain a similar mean coating thickness, the coating efficiency for smaller pellets was higher. As the final weight gain for all pellet sizes was not significantly different, the reason for a thicker coat for smaller pellets might be a better and faster application of the coating formulation, which results a thicker but less dense coating structure compared to larger pellets.

To further investigate the difference in CT between batches, the average TEFPS values from all batches were compared. TEFPS is sensitive to both signal loss due to scattering effects on a rough coating surface and refractive index changes due to density changes. The mean TEFPS value from 6 mm pellets was 16.2% of the initial signal strength being reflected off the surface, whereas only 2.2 and 2.6 % were reflected from 2.5 and 1 mm pellets, respectively. Since no differences in the surface morphology between pellet batches could be found using SEM imaging, the effect of the surface morphology on the TEFPS values is likely to be small, However, the increase in curvature due to the decrease in size of the pellets may have lead to a signal loss similar to the signal loss identified in a previous study on biconvex tablets[10]. Therefore, the impact of signal loss and/or density changes on the TEFPS values is not directly resolvable.

As it can be seen in Figure 2, the relative drug release rate increased with decreasing pellet size. This can be explained by the higher surface area available for drug transport through the polymeric film coating. This surface area effect overcompensates the film coating thickness effect: As discussed above, smaller pellets exhibited a thicker polymer film coating, which leads to increased diffusion pathway length and, thus, slower drug release. The difference was statistically significant when comparing the 1 and 2.5 mm pellets with the 6 mm pellets (with f_2 values of 38 and 47, respectively). Pellets of 2.5 mm in diameter showed a slower drug release compared to 1 mm pellets, however, this was not statistically significant with a f_2 value larger than 50.

Figure 2. Dissolution rate of 10 pellets with 6 mm (blue triangles), 2.5 mm (red circles) and 1mm (black squares) in diameter ($\bar{x}$ ± SD, n = 10). SD = standard deviation



4. Conclusions

In conclusion, TPI investigations were successfully carried out to non-destructively image sustained release coated pellets with different sizes. CT, drug layer thickness and the TEFPS (surface morphology) measurements enabled a deeper insight into the coating characteristics of these pellets. The non-destructively obtained TPI data revealed differences in the coating thickness related to the pellets' size, and these observations were related to dissolution performance differences. The study suggests that analysis with TPI may be valuable in the optimisation of the coating process of multiparticulate drug delivery systems.

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