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Research paper

Terahertz pulsed imaging, a novel process analytical tool to investigate the coating characteristics of push–pull osmotic systems

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ABSTRACT

The aim of this study was to investigate coating characteristics of push–pull osmotic systems (PPOS) using three-dimensional terahertz pulsed imaging (3D-TPI) and to detect physical alterations potentially impacting the drug release. The terahertz time-domain reflection signal was used to obtain information on both the spatial distribution of the coating thickness and the coating internal physical mapping. The results showed that (i) the thickness distribution of PPOS coating can be non-destructively analysed using 3D-TPI and (ii) internal physical alterations impacting the drug release kinetics were detectable by using the terahertz time-domain signal. Based on the results, the potential benefits of implementing 3D-TPI as quality control analytical tool were discussed.

1. Introduction

Cellulose-acetate-based coatings have been commonly used as insoluble membranes in the formulation of modified-release medicines. Part of the oral modified-release technologies using cellulose-acetate-based films are the osmotically driven systems developed in the 1970s by Theeuwes and associates to deliver poorly soluble drugs independently of the GI mobility [1]. Push–pull osmotic system (PPOS) is one of the osmotically driven systems specially designed to deliver poorly soluble drugs. This technology typically consists of a bilayer tablet core surrounded by a laser-drilled semipermeable membrane [2]. As illustrated in Fig. 1, the semipermeable membrane controls the water ingress and thereby the swelling kinetics of the push layer which pushes the drug layer through the orifice. Therefore, small variations in the semipermeable membrane properties can affect the drug release performance of these systems.

Recently, a number of imaging and spectroscopic techniques have been suggested for the quality control of pharmaceutical products, including X-ray microcomputed tomography [3], Raman imaging [4,5], near-infrared imaging [6,7] and terahertz imaging [8,9]. Many of these techniques have yet to be applied to osmotically driven systems. Nevertheless, some limitations could be anticipated using either near-infrared imaging, X-ray tomography or Raman spectroscopy for studying PPOS. Indeed, the laser-excitation used in Raman imaging technique can destroy the polymeric membrane of the drug product; this coupled with the long data acquisition times are the major limitations of this technique. X-ray tomography has high running costs, issues with beam hardening towards the edge of products as well as the long data analysis times that will limit its application. The low penetration depth of near-infrared imaging generates the requirement for cross-sectioning of samples. It was, therefore, the aim of this study to evaluate the potential of the three-dimensional terahertz pulsed imaging (3D-TPI) to characterize, in a non-destructive manner, the spatial and statistical coating thickness distribution of PPOS. The terahertz time-domain waveform was also used to detect internal physical alterations due to interruptions during the coating process. This investigation was conducted based on the methodology successfully applied to the investigation of various coating systems such as controlled-porosity coatings [10–12] and cosmetic and enteric coatings [13]. The implementation of 3D-TPI as a in-process control (IPC) tool was finally discussed.

2. Experimental

2.1. Materials

The ingredients of the bilayer tablet core were isradipine, polyethylene oxides (PEO, Polyox WSR N-80 and WSR 303, Dow Chem-

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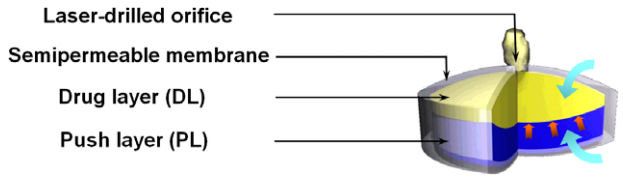

Fig. 1. Drug release mechanism from push–pull osmotic systems.

ical, Midland, US), sodium chloride (VSR AG, Pratteln, Schwitzerland), indigo blue (FD&C No. 2, Univar Ltd., Bradford UK), and magnesium stearate (FACI SRL, Carasco, Italy). Cellulose acetate (Mw 30 kDa, Eastman Chem. Prod., Kingsport, US) and polyethylene glycol (PEG 400, Clariant GmbH, Sultzbach, Germany) were the ingredients of the coating formulation. All the components were sieved through a 500-μm mesh sieve prior to use.

2.2. Tablet compression

Two tablet core formulations were prepared as summarized in Table 1. All ingredients of both the drug and the push layers were blended separately using a Turbula T2F shake-mixer (WAB AG, Basel, Switzerland) except the magnesium stearate which was added finally as external phase. The bilayer tablet cores were compressed on a single press (Korsch EK0, Berlin, Germany). The drug layer was compressed first with a pre-compression pressure of 0.5 kN. After the addition of the push-layer blend, a 6-kN compression force was applied. Round 8-mm biconvex tablet cores were finally obtained.

2.3. Tablet coating

The tablets were coated in a pan coater (Bohle BFC5, Ennigerloh, Germany) equipped with a two-fluid nozzle (Schlick, Coburg, Germany). The coating conditions are listed in Table 2. A coating formulation consisting of cellulose-acetate plasticized with 5% PEG and diluted to a concentration of 7.5% solids in acetone/water (95:5 v/v), was prepared and applied to the tablet cores. Process endpoints were fixed to targets of 10% and 20% of coating weight gain. Subsequently, a coating defect was simulated by interrupting the coating process. Thus, the coating process was stopped 30 min after spraying two-third of the coating solution. A final coating gain weight of 20% was finally reached. A 1 mm size orifice was manually drilled on the drug layer face of each tablet.

Table 1
Composition of the tablet cores.

Ingredients	Quantity (mg)	
	Formulation #1	Formulation #2
Drug layer		
Isradipine	5	50
PEO (Mw: 200 kDa)	155	110
NaCl	25	25
Magnesium stearate	2	2
Push layer		
PEO (Mw: 7000 kDa)	60	60
Indigo blue	1.5	1.5
Magnesium stearate	1	1

Table 2
Coating conditions.

Tablet batch quantity (kg)	1.2
Inlet air temperature (°C)	30
Fluid bed/nozzle distance (cm)	7
Chamber air flow ($Nm^3\ h^{-1}$)	100
Spray rate ($ml\ min^{-1}$)	16
Spray air pressure (bar)	0.7
Atomization air pressure (bar)	0.7
Rotation rate (rpm)	14

2.4. Terahertz pulsed imaging

Terahertz 3D data of tablets under investigation were recorded using TPI Imaga 2000 (TeraView, Cambridge UK). The operation of this instrument had been previously reported [13]. Briefly, an ultrashort terahertz pulse is generated by the instrument; when it encounters a tablet surface or tablet coating, this pulse is reflected back to a time-gated terahertz detector. The resulting terahertz waveform thus consists of multiple pulses arriving at the detector at delayed time points depending on the index of refraction and the thickness of the penetrated layer, see Fig. 2. The pulses generated by this technique have an extremely low average power (<100 nW), and therefore do not destroy the polymer membrane within the product. As most pharmaceutical ingredients are semi-transparent to terahertz radiation, pulses can penetrate several millimetres into final dosage forms and thereby eliminate the need to tablet cross-section [13].

Terahertz 3D data set maps (x-direction, y-direction and z-direction) comprising different number of point measurements with 200 μm point spacing were recorded. About 1400 pixels on the tablet-face and -end surfaces were scanned, and the measurement took in the region 15-min per surface. Terahertz waveform consisting of 512 data points was recorded at each point of the image.

2.5. Coating thickness determination

The tablets were cut in the centre to determine the membrane thickness using optical microscopy (Sterni V11 Zeiss, Jena, Germany). The average coating thickness for each batch was calculated based on six tablets with a 66× focus with AnalySIS v5.1 (Soft Imaging System GmbH, Muenster, Germany). The coating thickness average was defined as the mean value of 20 measurements uniformly distributed around the tablet.

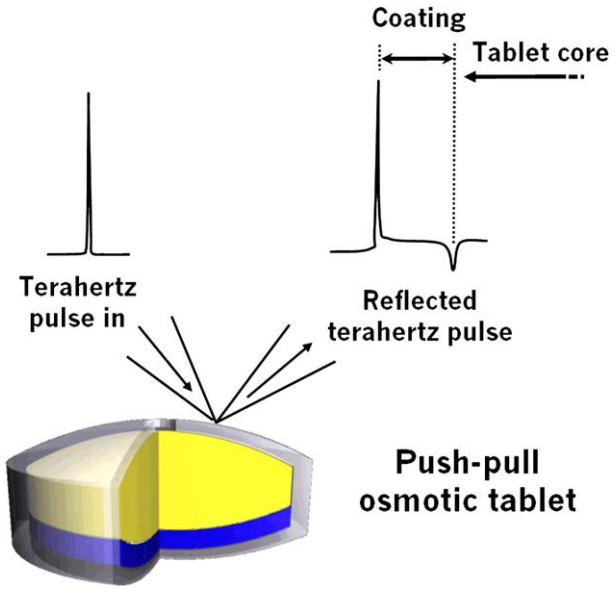

Fig. 2. Schematic diagram of the experimental arrangement to examine coating of push–pull osmotic systems.

Table 3
Thickness measurements by 3D-TPI vs optical microscopy.

Tablet core	Coating weight gain (%)	Thickness averages[b] measured by		Two-tailed, paired *t*-test		
		3D-TPI ($n = 4$)	Microscopy ($n = 6$)	*t*	*p*	Result[a]
Formulation #1	9 ± 0.5	112 ± 6	112 ± 3	0.112	0.91	*N*
Formulation #2	10 ± 0.3	119 ± 7	114 ± 5	1.245	0.24	*N*
Formulation #2	18 ± 1.3	268 ± 5	259 ± 7	2.150	0.06	*N*

[a] *N* means not significantly different at 0.05 level.
[b] Data described as average ± standard deviation. List of figures.

2.6. Dissolution test

The *in vitro* isradipine dissolution test was carried out on six tablets per batch using USP dissolution apparatus I (Varian, Edison, US) with a basket rotation speed of 100 rpm. The dissolution medium was buffered at pH 6.8 and 0.2% of lauryldodecylamine-*N*,*N*-oxide was added to reach sink condition. Samples were collected every hours over 16 h and were analysed according to isradipine USP 30 monograph by High Performance Liquid Chromatography with UV-detection at 328 nm wavelength (Waters, Milford, US). The dissolution profiles were also individually compared using both the "difference factor, f_1" [14] and the "similarity factor, f_2" [15,16] defined as Eqs. (1) and (2)

$$f_1 = \left(\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right) \times 100 \quad (1)$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t \cdot (R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the sample number, w_t is an optional weight factor, R_t is the reference assay and T_t is the test assay at time point t.

3. Results and discussion

3.1. Coating thickness measurement

The coating thickness average determined by terahertz pulsed imaging (TPI) was primarily validated *versus* the optical microscopy destructive measurements. A comparison of the average thicknesses from three batches is shown in Table 3. Thickness measurements performed by terahertz and microscopy were not significantly different (*t*-test, $\alpha = 0.05$). TPI measurements were also repeated on tablets with different tablet cores coated at the same time. It appears that the tablet core composition did not influence the coating thickness distribution as shown in Fig. 3. Nevertheless, it was observed that the thickness distribution was not truly uniform around the tablets. More specifically, the coating thickness of the tablet central band was 30% thinner than the tablet face in case of the batch with 10% of film coat. Similar observation was reported by Ho and co-workers for bi-concave tablets coated with a 150-μm poly(vinyl-acetate)-based film with a 33% thinner central band [10,12]. Authors hypothesized that the difference was possibly due to either the TPI-signal distortion or the measurement coating layer thickness discrepancy. Interestingly, no significant difference was further observed for 20% coating gain, despite an extremely low variation of tablet shape. Therefore, the present results seem to exclude that the difference is due to thickness determination method. As already hypothesized in the previous publication [12], the coating thickness difference is probably due to the tablet shape which leads to a statistically longer spray exposure time of tablet face during the tablet rolling in the coater pan.

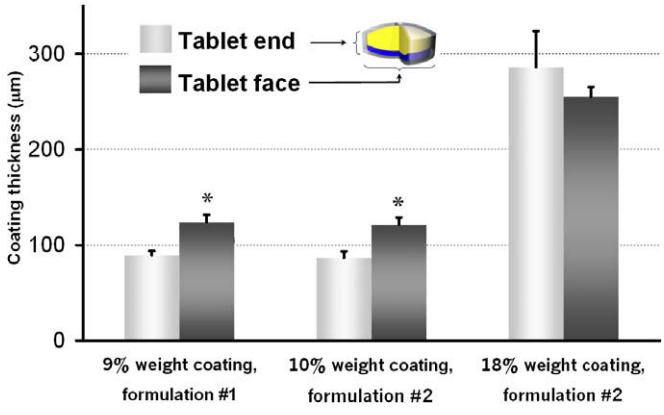

Fig. 3. Coating thickness of the tablet faces and ends varying in either the tablet core or the coating gain weight.

3.2. Prediction and detection of coating quality deviations affecting the drug release performance

The drug release profile of formulation #1 was determined and correlated with the TPI measurements. The drug release rates were 8%/h and 5%/h for the tablets with 10% and 20% film coat weight, respectively. By linearly correlating the thickness and the drug release data, it can be estimated that a variation of 10 μm thickness average (1% weight gain) leads to a deviation of 0.3%/h drug release rate. It is therefore important to keep under control the coating thickness which directly impacts on the drug release profile.

Furthermore, the coating process can also influence the drug release performance as demonstrated by simulating a 1-h interruption. Fig. 4 shows that the drug release profiles of both formulations #1 and #2 were significantly decreased for those tablets that had been discontinuously coated ($f_1 > 15$ despite $f_2 > 50$). Interestingly, an internal coating interface was detected on the terahertz domain waveform and was confirmed by optical micros-

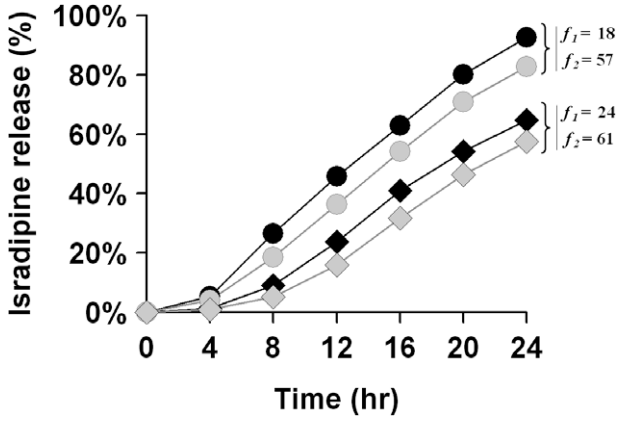

Fig. 4. Dissolution profiles either with (● and ♦) or without (● and ♦) coating process interruption of formulations #1 & #2, respectively ($n = 6$, error smaller than symbols).

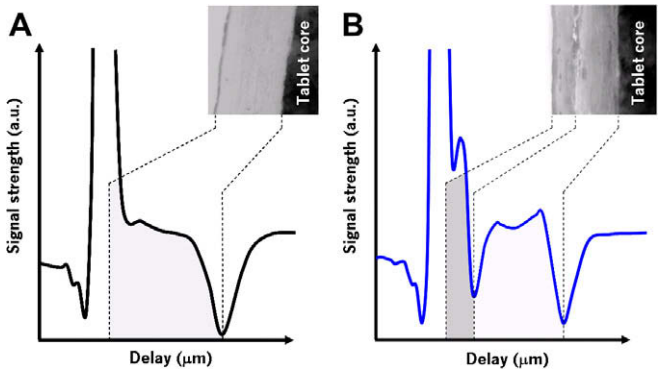

Fig. 5. Time-domain waveform allowing the detection of internal alteration due to coating process interruption: spectra without and with internal physical alteration in (A) and (B), respectively.

copy as shown in Fig. 5. Furthermore, the coating interface was located at a depth of about 120 μm below the surface, which corresponded to the one-third proportion sprayed after the interruption. An additional curing step in the coating process attenuated the interface creation, but only partially reduced the effect of the coating step interruption on the drug release performance.

3.3. Potential applications of 3D-TPI strengthening the PPOS development

Already presented by US Food & Drug Administration analytical experts as an "attractive replacement of wet dissolution testing" for delayed-release tablets [12], the present study opens new perspectives to ensure the quality along the development of PPOS. Controlled by the coating properties, the presented study highlights the importance of evaluating the coating properties to predict the drug release performance of PPOS. The interest in developing imaging techniques has grown in the recent few years with the raising complexity of new PPOS, e.g. methylphenidate PPOS (Concerta™) [17] consisting of a tri-layer tablet core and tri-layer coating. The root-cause analysis of drug delivery deviations becomes quite difficult by only using dissolution tests. Already tested on multilayer systems [9,13], 3D-TPI could potentially be used during pharmaceutical development to detect non-destructively and concurrently (i) variations of the coating and/or drug over-coating thickness and properties and (ii) delamination issues during the tablet core compression [9,18]. In the same setting, information on the drilling quality may also be collected as illustrated in Fig. 6. Therefore, the non-destructive nature of the TPI measurements could potentially benefit to strengthen the quality control during the development and manufacturing of PPOS. However, further work is required to address the correlation of information provided by TPI images to each of these physical product performances.

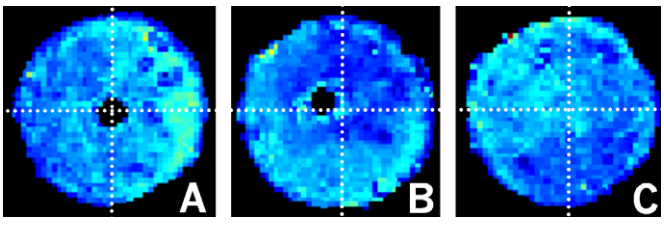

Fig. 6. Terahertz 2D mapping of the drug layer allowing to determine the drilling quality: (A) tablets drilled with a centred orifice; (B) the non-centered and smaller orifice; and (C) not drilled tablet.

4. Conclusions

In this study, the membrane characteristics of push–pull osmotic systems were investigated using the novel 3D-terahertz pulsed imaging technique. Intra- and inter-PPOS membrane variations were non-destructively detected. Thickness distribution variations were correlated with the drug release kinetics to better predict the effect of thickness variations on the release performance. In addition to spatial information, a mapping was also performed to get a profound understanding of the membrane physical properties. Internal physical changes leading to lower release kinetics were detected and further explored. The implementation of terahertz pulsed imaging as quality control analytical tool in the development and the manufacturing may represent a major step forward to improve the design, the scalability and potentially the quality control during the routine manufacture of push–pull osmotic systems.

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