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Developing a Fast, Non-Destructive Terahertz Dissolution Assay of Tablets During Manufacture

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PURPOSE

To achieve a continuous downstream manufacturing process with on-line quality monitoring and real-time release, different process analytical technology (PAT) methods, such as near infrared (NIR) [1-3] and Raman [3] spectroscopy, can be deployed to predict the dissolution, disintegration, hardness, content uniformity and particle size amongst others.

However, the use of the above methods to reliably predict dissolution and disintegration rate of tablets is quite challenging. This is due to the inability of above methods to directly measure and quantify the physical properties, e.g. porosity, that directly govern the mass transport processes in tablets during dissolution and disintegration [4, 5].

Terahertz time-domain spectroscopy (THz-TDS) has been used to reliably measure the porosity of tablets [6, 7] without chemometric analysis. The terahertz porosity method is fast (under a second), non-destructive and will allow real time release testing (RTRT) of tablets during manufacture.

This study therefore demonstrates the promising correlation observed between porosity, dissolution, disintegration and tensile strength of pharmaceutical tablets measured by terahertz time-domain spectroscopy.

MATERIALS

Five batches, ibuprofen (10% w/w), of biconvex tablets with a typical blend were directly compressed using a compaction simulator (HB50, Huxley Bertram Engineering Ltd, UK).

The targeted porosity range for the batches was achieved by keeping the weight of all tablets at 400 mg and adjusting their thickness (see Table 1).

Batch	H (mm)	d (mm)	W (mg)	$f_{nominal}$ (%)
B1	4.678	10.057	396.5±3	7.22±0.21
B2	4.878	10.061	397.2±2	11.83±0.22
B3	5.060	10.067	396.9±2	15.85±0.33
B4	5.276	10.083	396.7±2	20.20±0.48
B5	5.528	10.089	409.0±3	22.41±0.57

Table 1: The average nominal porosity, $f_{nominal}$, is calculated from the physical dimensions, i.e. thickness, H, diameter, d, as well as weight, W, and the the true density of the batches of the formulation.

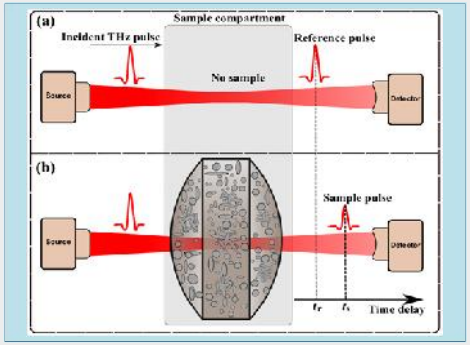
METHODS

Terahertz measurements of the batches were acquired using a TeraPulse 4000 (TeraView Ltd., Cambridge, UK).

The effective refractive index, n_{eff}, is measured using the terahertz pulse delay, Δt, and the speed of light in vacuum, c (Eq. (1)). The terahertz porosity, f_{THz}, of the tablets was extracted from n_{eff} using the the anisotropic Bruggeman's effective medium approximation (Br-EMA) [6].

$$= \frac{\Delta}{} + \quad (1)$$

Figure 1. Sample and reference measurements.

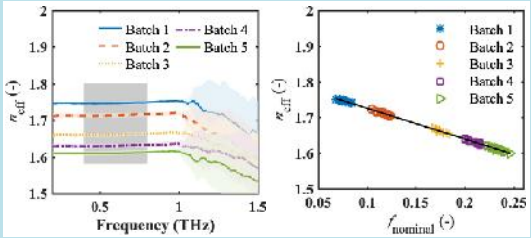


Material Characterization

The intrinsic refractive index of the formulation, i.e. the refractive index of only the solid material of the tablets was measured using similar batches of flat-faced tablets of the same formulation.

The effective refractive index is selected from a range of frequency and used for measuring the intrinsic refractive index of the formulation using the Br-EMA [6].

Figure 2. Material characterization using flat-faced tablets. The measured n_{solid} = 1.810 with R^2 = 0.999 and RMSE = 0.0017.



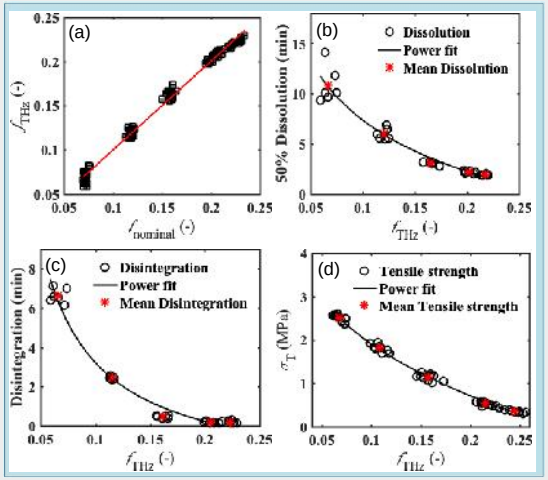
RESULTS

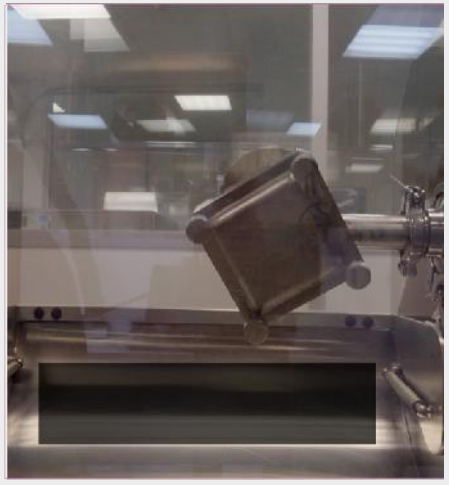
Figure 3 (a) showcases the excellent linear correlation observed between the predicted terahertz porosity, f_{THz}, and the nominal porosity, $f_{nominal}$, (data for the embossed tablets not shown).

The measured dissolution time at 50% of the drug released, the disintegration time and the tensile strength, , were correlated with THz porosity.

Figure 3 (b)-(d) show the promising correlation between the THz porosity and the three most significant quality parameters of pharmaceutical tablets.

Figure 3. A correlation between measured THz porosity and tablet properties





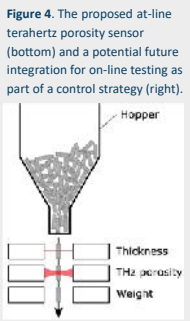
CONCLUSIONS

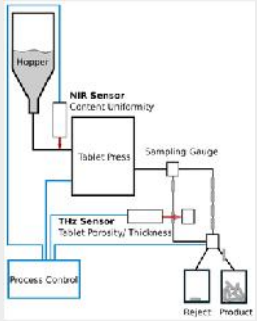
The excellent linear correlation observed between the nominal and the terahertz porosity manifests the robustness of the terahertz approach for tablet porosity measurement even for tablets containing high absorbing API (ibuprofen) as well as embossing.

The promising correlation of the terahertz porosity with dissolution, disintegration and hardness manifest the unique ability of using the terahertz porosity method for real time dissolution assay of tablets during manufacture.

We are currently developing a fully automated at-line terahertz porosity sensor that can quickly predict the dissolution, disintegration and hardness of hundreds of tablets fed from a hopper as shown in **Figure 4**.

Figure 4. The proposed at-line terahertz porosity sensor (bottom) and a potential future integration for on-line testing as part of a control strategy (right).





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