Pharmaceutical Tablet Hardness Measurements with THz Pulsed Imaging

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***Abstract*— We present the results of terahertz pulsed imaging (TPI) experiments to measure the 'hardness' of pharmaceutical solid dosage forms (tablets) compacted at various compression forces. Results of TPI measurements are compared to those from diametric compression tests as well as finite element analysis (FEA) simulations of density distributions on the surface of the tablet. In both cases strong correlation with TPI results was found. In particular, radially symmetric spatial distributions in tablet density due to the shape of the punch used in tablet manufacture were observed. The results of these experiments show that TPI is suitable for non-destructive monitoring and control of pharmaceutical manufacturing processes.**

I. Introduction

TERAHERTZ-PULSED imaging provides a means of non-destructively measuring various metrics critical to pharmaceutical tablet manufacturing. For instance, TPI has recently been used for nondestructive and quantitative characterization of pharmaceutical tablet coatings[1]. Another important processing parameter that requires precise detection and control is the tensile strength (an indirect measure of particle bond strength) of a compressed tablet. Over a finite range of applied compression forces, a tablet's tensile strength varies approximately linearly with compaction force. However, outside this range tablet failure can occur for a number of reasons. For example, a tablet must have sufficient tensile strength to maintain integrity in post-compaction processes, such as tablet coating, as well as packaging and shipping. Conversely, during compression of cylindrical tablets, excessive compaction force can result in tablet failure due to a phenomenon called capping. In this case an intensive shear band is formed between the top edges and the mid-center of the tablet and results in the top of the tablet separating from the rest.

Here we show how TPI can be used to measure the surface refractive index (SRI) of a tablet, which provides an indicator of surface density[2], which in turn is closely related to tensile strength. The surface refractive index at a point i on a tablet surface is given by $n_i = n_s(1+S_i)/(1-S_i)$, where n_s is the refractive index of the surrounding medium (in this case air) and S_i is the peak intensity (relative to the baseline intensity) of the terahertz pulse $s_i(t)$ reflected from that point.

As well as conducting TPI measurements, the tensile strength of sample tablets was measured using a traditional diametric compression test[3]. An increasing force is applied to the centre of a tablet until it breaks. Besides its destructive nature, this test provides only an indicator of the tensile strength of the tablet as a whole; it yields no information on the spatial distribution of tensile strength. Furthermore, the empirical equation that relates the crushing force (or tablet hardness) to tensile strength applies only to flat-faced tablets but not to commonly used convex tablets, or those with embossed surfaces. TPI can address these issues by making closely-spaced point-by-point measurements over the entire tablet surface.

II. Results

Eight batches of twenty 14 mm diameter pharmaceutical bi-convex tablets were compacted (from lactose powder with 1% magnesium stearate added as blend) on a tablet press (XSpress R&D, Oystar-Manesty, Merseyside, UK) under eight different compression forces between 3.13 kN and 23.16 kN. Each station on the tablet press is fitted with a strain gauge that was used to measure the force applied during powder consolidation. After compaction, 10 tablets were subjected to a diametric compression test. TPI measurement of the remaining 10 tablets were made using a TPI Imaga 2000 (TeraView Ltd., Cambridge, UK). For TPI measurements, time-domain terahertz pulses reflected from nearly uniformly spaced points on the non-embossed convex surface of each tablet were recorded at 0.2 mm intervals. This produced a two-dimensional time-domain waveform map (consisting of approximately 2,600 data points) of the surface of each tablet. The spatial distribution of the surface refractive index of each tablet was then calculated. Figure 1 shows SRI maps of six tablets compressed at 3.13 kN.

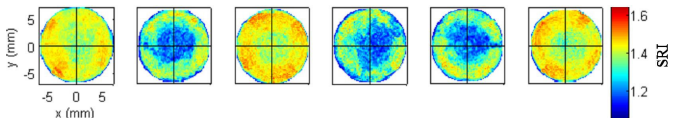

Figure 1: Surface refractive index (SRI) maps from six 14 mm diameter, bi-convex tablets compressed at a compaction force of 3.13 kN.

When plotted against compaction force, the average SRI for each tablet follows a trend similar to that of the crushing force measured during diametric compression tests (Figure 2). Both crushing force and SRI increase exponentially with compaction force until a plateau is reached – in this case at approximately 23 kN. Tablets compacted at forces exceeding this value are liable to failure by capping. Note the considerable variation in average SRI, as well as the crushing force, of individual tablets

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at each compaction force. This variability may indicate either an inconsistency between expected and actual applied compaction force at each station in the tablet press that was used to make the tablets or perhaps a lack of repeatability in the compaction process at each station. In any case, TPI is clearly capable of non-destructively distinguishing between sample tablets that have different surface refractive indices, thus demonstrating the potential that exists for applying TPI to tablet hardness analysis during tablet manufacture.

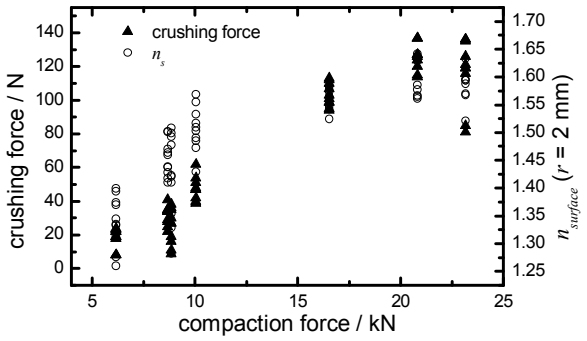

Figure 2: Crushing force and average surface refractive index (SRI) of ten sample tablets compacted at eight different compression forces.

As well as the large variation in the average SRI at each compaction force, the spatial distribution of SRI across the surface of individual tablets is inhomogeneous, as is clearly illustrated by the SRI maps shown in Figure 1. Analysis of the surface variation shows that SRI is radially symmetric and increases non-linearly as a function of tablet radius, as is shown in Figure 3.

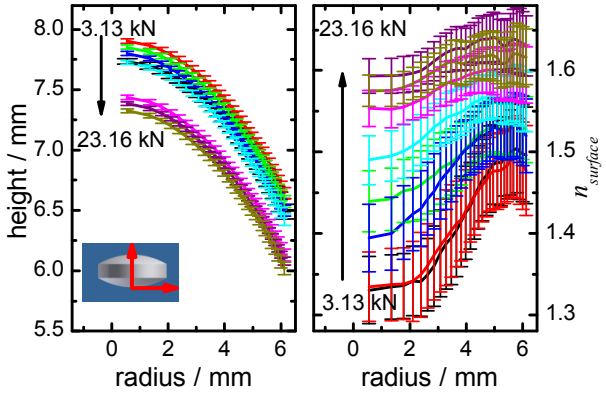

Figure 3: Radial analysis of measured TPI data showing averaged tablet surface height (left) and surface refractive index (right) of 10 sample tablets at each of the 8 compression forces (3.13 to 23.16 kN).

This spatial distribution can be explained by variations in tablet density due to local tablet geometry imposed by the shape of the tablet punch, as well as properties of the materials used in tablet compaction. To this end, a finite-element computational compression simulation[4] was used to model the density distribution of the powder during tablet compression.

A cross-sectional slice through the tablet density map at a simulated compaction force of 22.2 kN is shown in Figure 4. Comparison of the trends in SRI and the predicted density as a function of tablet radius is shown in Figure 5.

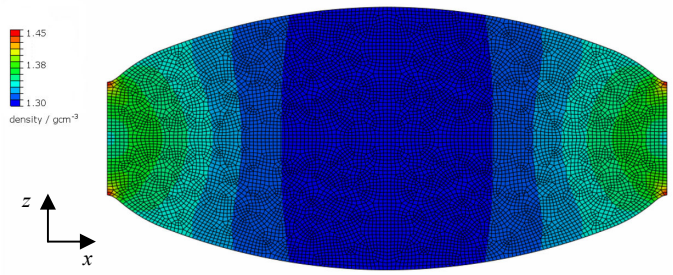

Figure 4: Cross-sectional slice of simulated density distribution through the body of a 14 mm diameter tablet compressed under a compaction force of 22.2 kN.

In general, the trends in simulated surface density and measured SRI are in close agreement and any differences are easily accounted for. For example, the higher rate of increase in simulated surface density is due to using a relatively small value for the die wall coefficient of friction used in simulations.

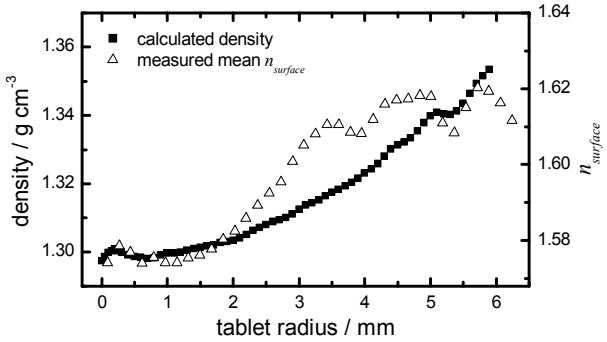

Figure 5: Comparison of measured tablet surface refractive index, n_s and simulated surface density as a function of tablet radius.

Acknowledgements

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