Terahertz Pulsed Imaging of Surface Variations on Pharmaceutical Tablets

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***Abstract*— We present an analysis of terahertz pulsed imaging (TPI) measurements made on pharmaceutical tablets compacted at a range of compression forces. In particular, we investigate the uniformity and local variations in the refractive index on the surface of tablets of different shapes. Through terahertz imaging it has been possible to observe small-scale deviations on tablet surfaces that may have relevance to the quality of tablet manufacture and performance.**

I. Introduction

In pharmaceutical manufacturing, tablet surface quality is important for the effectiveness of subsequent film-coating during the production of modified release tablets. The surface of a tablet must be sufficiently smooth so as to minimize mutual chipping of tablets, yet rough enough to allow for adhesion of liquid droplets to the tablet core. Furthermore, the surface density distribution of the core must have sufficient uniformity so that the interaction between sprayed droplets and the core surface is consistent across the tablet. We have previously shown[1] how terahertz pulsed imaging (TPI) can be used to measure the average surface refractive index of pharmaceutical solid dosage forms and how this varies as a function of the compression force at which tablets are compacted on a tablet press. In that study it was also shown that surface refractive index is inversely proportional to the surface height, such that a circularly-symmetric tablet whose surface height varies smoothly as a function of tablet radius will have a refractive index distribution that also varies with radius (Fig. 1). In this paper we investigate localized spatial variations on the surface of pharmaceutical tablets.

II. Results

TPI measurements of two batches of compressed pharmaceutical tablet cores (compacted on an Xpress R&D rotary tablet press from OYSTAR Manesty) were made using an Imaga 2000 (from TeraView Ltd.). The first batch consists of tablets with flat upper and lower surfaces and beveled edges, the separation between which is inversely proportional to the force at which tablets were compacted; the second batch of tablets have convex upper and lower surfaces.

Fig. 2 shows the terahertz images from one surface of a bi-convex tablet that was compacted from lactose monohydrate powder at a compression force of 23.16 kN. For each tablet two maps are acquired: a two-dimensional map of the tablet surface height (upper-left, Fig. 2), as measured using a laser gauge, and the corresponding terahertz surface refractive index distribution (lower-left, Fig. 2). TPI measurements were made on a total of 12 tablets compacted at the same compression force. From all twelve measurements, representative 2-D maps of surface height and refractive index were calculated (centre, Fig. 2).

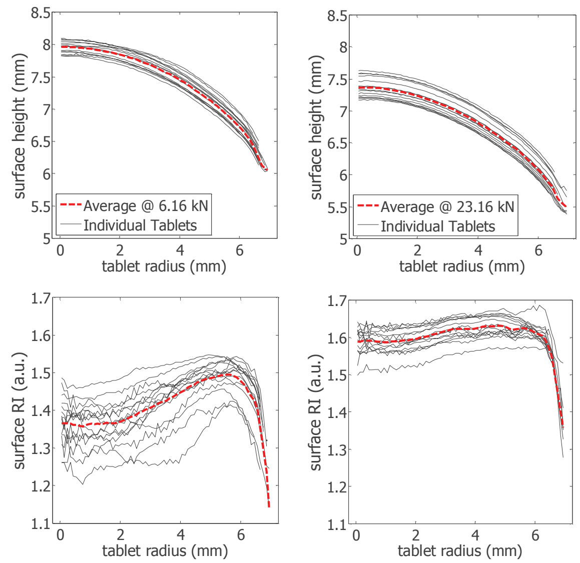

Fig. 1. Measured one-dimensional profiles of surface height (**top**) and surface refractive index (**bottom**) as a function of tablet radius for bi-convex tablets compacted at 6.16 kN (**left**) and 23.16 kN (**right**). Solid black lines represent measured profiles from fifteen individual sample tablets at each compression force; dashed red lines represent the average of the 15 measured profiles. The averaged 1-D profiles were revolved about the origin (tablet radius = 0 mm) to generate 2-D profiles that are representative of the surface height and refractive index at the relevant compaction force.

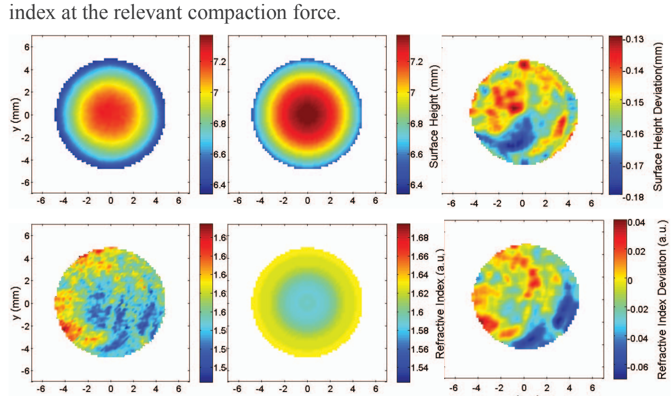

Fig. 2. Surface height (**top**) and refractive index (**bottom**) from a bi-convex tablet compressed at 23.16 kN. Measured profiles (**left**), averaged profile for tablets at same compression force (**centre**) and deviation from average (**right**).

The difference between these 'averaged' maps and those from individual tablets provide a means of visualizing any local deviations (right-hand side, Fig. 2). It is clear from these figures that peaks in refractive index correspond to dips in surface height and vice versa.

Scatter plots of surface refractive index deviation as a function of surface height deviation for five tablets compressed at five different compaction forces are shown in Fig. 3. Notice that while the degree of scatter in surface height deviation does not change considerably between different compaction forces, the scatter in refractive index deviation clearly decreases at higher compaction forces. Fig. 4 shows the average and standard deviation of scatter in both surface height and surface refractive index deviation for all sample bi-convex tablets (up to fifteen tablets at eight different compaction forces between 3.13 and 23.16 kN). We conclude that for these tablets, uniformity in surface refractive index increases with compaction force and possibly reaches an upper limit at the highest compaction forces.

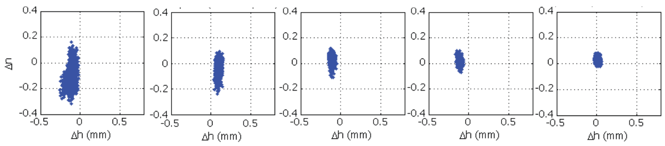

Fig. 3. Scatter plots of surace refractive index deviation, Δn as a function of surface height deviation, Δh for individual sample bi-convex tablets compacted at compression forces of 3.13, 8.68, 10.05, 16.54 and 23.16 kN. The amount of scatter in the y-direction (surface refractive index deviation) decreases at higher compaction forces.

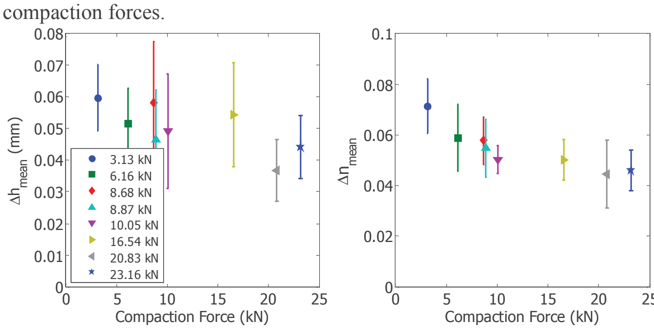

Fig. 4. Scatter in deviation of surface height (**left**) and surface refractive index (**right**) for twelve bi-convex tablets at eight different compaction forces.

The same analysis was applied to data obtained from a set of flat-faced tablets that were compressed over a similar range of compression forces. The results, shown in Fig. 5, are noticeably different to those from the bi-convex tablets. In this case, the degree of scatter in both surface height deviation and refractive index deviation is negligible compared to that seen for the set of bi-convex tablets, which indicates that a much greater degree of surface accuracy can be attained in the manufacture of flat tablets. This may be because the flat-faced punches can themselves be machined to a higher level of accuracy and repeatability than punches with curved surfaces. The only exception occurs in tablets that were compressed at two of the lower forces. Inspection of the scatter plots in Fig. 6 from individual tablets compacted at four of the eight compaction forces reveal large variations in surface refractive index deviation with similarly high variations in surface height deviation for tablets compacted at 7.0 and 11.0 kN. Two-dimensional maps of these particular tablets reveal the existence of a small number of isolated regions in which surface height is greater than the average and surface refractive index is lower than the average. For example Fig. 7 shows maps of surface height and refractive index for the tablet compacted at 11.0 kN, the scatter plot of which is presented in Fig. 6. The small raised areas are randomly located on the tablet surfaces and occur on just a few tablets. It is unlikely that this is due to irregularities in the punch face, since all sample tablets were pressed on a tablet press with only four tabletting stations. Thus if these small deviations were due to the faulty punches we would expect not only to observe them on a greater number of tablets, but also to see their locations within each tablet being repeated from tablet to tablet. We thus conclude that the source of these local variations in the tablet surface is external to the tabletting stations used. Rather, it is possible that these small raised areas are due to relaxation of the compacted powder after ejection from the tablet press or insufficient lubrication. These small raised areas may impact negatively on tablet performance and integrity by, for example increasing the likelihood of mutual chipping or leading to coating defects in subsequent manufacturing processes such as film coating.

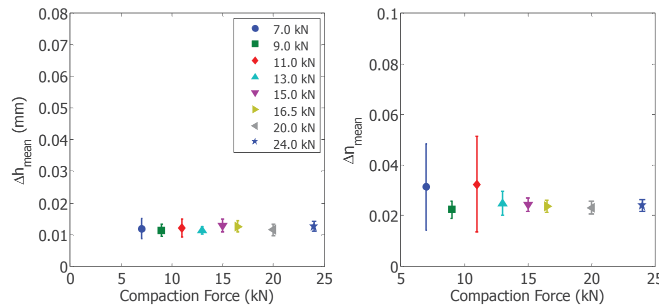

Fig. 5. Scatter in deviation of surface height (**left**) and surface refractive index (**right**) for fifteen flat-faced tablets at eight different compaction forces.

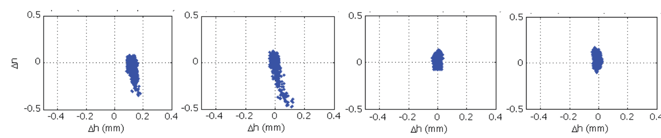

Fig. 6. Scatter plots of surace refractive index deviation, Δn as a function of surface height deviation, Δh for sample flat-faced tablets compacted at compression forces of (from left to right) 7.0, 11.0, 15.0 and 24.0 kN. The particular tablets compressed at the two lower compaction forces exhibit significantly more scatter in the y-direction (surface refractive index deviation).

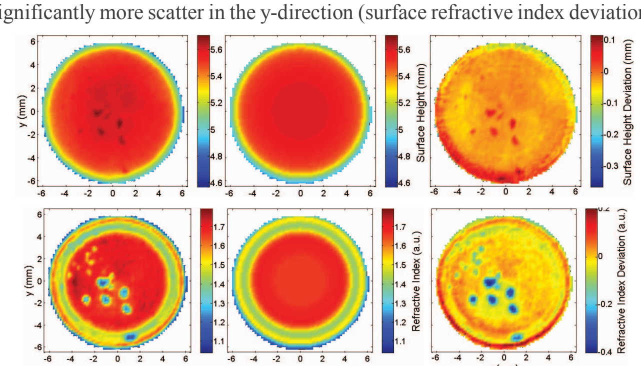

Fig.7. Maps of surface height (**top**) and refractive index (**bottom**) from a particular flat-faced tablet that was compacted at 11 kN and that contains small raised areas on its surface, which correspond to regions of relatively low refractive index. Shown here are maps of measured profiles (**left**), averaged profiles for all tablets compacted at 11.0 kN (**centre**) and maps of deviation from the average for this particular tablet (**right**).

References

[1] R.K. May, J. Alton, S.C. Zhong, L.H. Han, J.A. Elliott, D. Dey, L.F. Gladden, M. Evans, Y.C. Shen and J.A. Zeitler, "Pharmaceutical tablet hardness measurements with THz pulsed imaging", Proceedings of the IEEE International Conference on Infrared, Millimeter, and Terahertz Waves, Busan, South Korea, 21-25 September 2009.