# Non-destructive density measurements of pharmaceutical products by THz imaging

Joakim Garcia-Wernersson[1,2], Helena Rodilla[1], Alvaro Diaz-Bolado[2], Robin Dahlbäck[1], Lubomir Gradinarsky[2], Mats Josefson[2], Jan Stake[1]

[1]Chalmers University of Technology, Gothenburg, Sweden.
[2]AstraZeneca, Gothenburg, Sweden

*Abstract*—**In this paper, measurements with a THz imaging system at 346 GHz together with electromagnetic simulations have demonstrated the capability of THz sensing for the non-destructive density determination of intermediate products in the pharmaceutical industry. The results confirm the ability of THz imaging to detect density changes in pharmaceutical samples by measuring the phase variation of the wave transmitted through the sample.**

## I. INTRODUCTION

In the pharmaceutical industry, the roller compaction process is an intermediate state in the tablet manufacturing process that produces agglomerate strips which are often referred to as a ribbon. One of the key parameters of the roller compaction process is the density of the ribbons since it will affect the final quality of the manufactured tablets.

Located between microwaves and photonics, imaging in the THz frequency range (0.3 THz to 3 THz) offers higher resolution than microwave frequencies and higher penetration depth than the visible light. In this work we demonstrate the possibility of using THz imaging, a non-destructive technique, for the density measurements of the ribbons as an alternative to the currently used destructive methods.

## II. RESULTS

A continuous wave THz imaging system operating at 346 GHz has been used in this study [1]. The system consists of an emitter and a receiver with two antennas facing each other. The sample holder is located between the two antennas. The setup is mounted in a mechanical system that allows the scanning of the sample by moving the emitting and receiving antennas independently. Two different types of samples were used in this study, flat ribbons and patterned ribbons (see Fig.1). The patterned ribbons have a flat side while in the other side have a pattern consisting of half cylinders with a radius of 0.35 mm that intersect at 60° and 120°. This shape is created during the roll compaction process to increase the friction coefficient between the powder and the roll [2].

In this work we demonstrate the possibility of estimating the density of the ribbons by measuring the relative variations in the phase of the transmitted signal (i.e. with respect to an empty system). Electromagnetic simulations of the system with flat ribbons with permittivities between 2.2 and 2.8 and thicknesses with values between 0.84 mm and 1.99 mm have been used in order to study the effect that a change in permittivity has in the phase of the transmitted wave. The simulation results can be seen in Fig. 2. From these results, it is possible to model the relationship between the permittivity
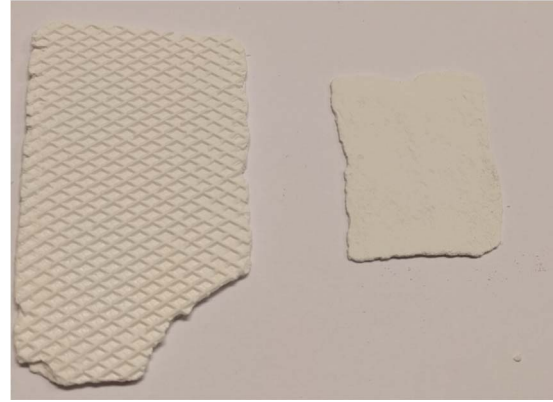


**Fig. 1.** Patterned ribbon (left) and flat ribbon (right).

of the ribbon ($\varepsilon'$), the sample thickness (d) and the phase change ($\Delta\phi$) using a polynomial model:

$$\Delta\phi = p_{00} + p_{01}\,\varepsilon' + p_{10}d + p_{11}d\varepsilon' + p_{20}\,d^2 \qquad (1)$$

we obtain that $p_{00}$, $p_{01}$, $p_{10}$, $p_{11}$ and $p_{20}$ are 22.0°, -9.2°, -179.3°/mm, 174.6°/mm and 4.5°/mm² respectively. This model includes the effects of multiple reflections and the sample holder.

The relationship between the permittivity, the change of phase and sample thickness has been obtained from the simulations. The next step is to obtain the relationship
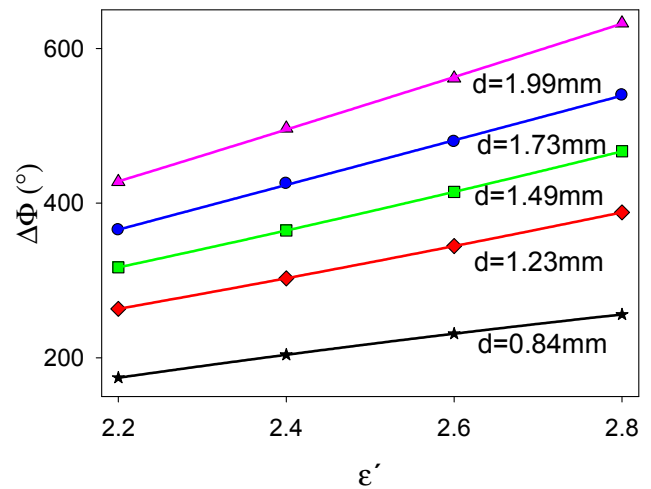


**Fig. 2.** Simulation results of the change of phase induced by a change in the sample permittivity for flat samples with thicknesses of 0.84 mm (black line, stars), 1.23 mm (red line, diamonds), 1.49 (green line, squares), 1.73 mm (blue line, circles) and 1.99 mm (pink line, triangles).
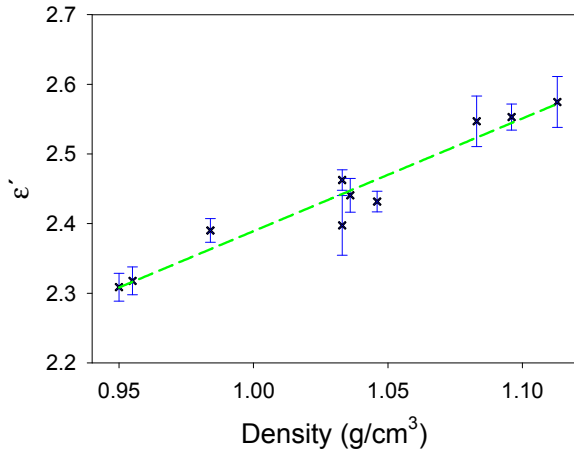
**Fig. 3.** Dielectric permittivity versus bulk density for paracetamol flat ribbons.



**Fig. 5.** Simulation results of a hypothetical sample with a permittivity variation in the x direction of 0.05 per millimeter. The colorbar represents the phase in degrees. The sample is 2 mm thick and the permittivity has a value of 2 at x=0.

between the permittivity and the samples density.

Ten paracetamol flat ribbons with known thicknesses and densities [2], all of them fabricated in AstraZeneca have been measured with our 346 GHz THz system. Measurements were taken in a 4 mm x 4 mm area with a spacing of 0.2 mm between consecutive measurement points. Fig. 3 shows the permittivity versus density for the measured flat ribbons. The permittivity has been obtained from the measurements results of the change of phase applying eq.1. The results obtained satisfy a quadratic relationship between density ($\rho$) and permittivity in the form $\varepsilon' = 1 + a\rho + b\rho^2$ [3], which in the range of densities under study can be consider linear. These results show the capability of THz imaging for the non-destructive density measurements of pharmaceutical products. The error bars in Fig. 3 account for the 5° drift in the measured phase observed in our system.

A similar study was performed with the patterned ribbons. The result for the relationship between the permittivity and the density for the patterned ribbons can be seen in Fig. 4. As can be observed, the estimated error is considerably higher in the case of the patterned ribbons compared to the flat ribbons. In the case of the patterned ribbons, in addition to the 5° error consequence of the drift of the measurements setup, other
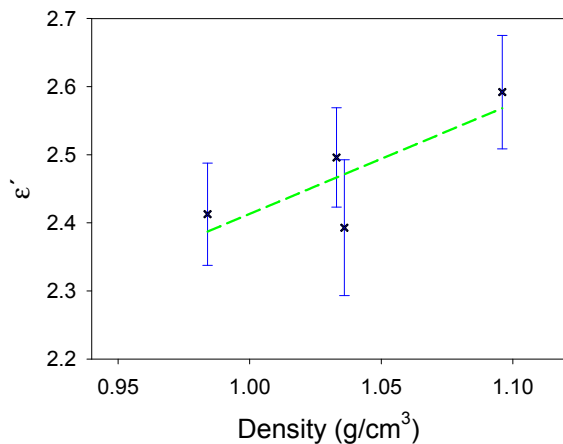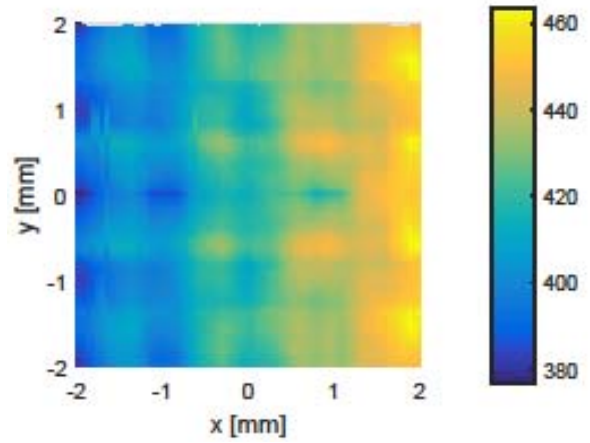
sources of error must be considered. In this case, the measurements are sensitive to how the patterned ribbons are placed in the sample holder. Simulation results have shown that a small translation along an axis, undetectable by eye, may cause a change of phase up to 8° and a rotation smaller than 10° is translated into a change of phase of 8°. This makes the estimated error 21° for the patterned samples.

As can be observed when comparing Fig. 3 and Fig. 4, similar results are obtained for the flat and for the patterned ribbons. This was expected as both types of ribbons were fabricated from the same formulation.

In order to study the validity of this imaging system to detect changes of density along the ribbons, simulations of samples with non-homogenous permittivity distributions were performed. Fig. 5 shows the simulated phase for a sample which permittivity increases 0.05 per millimeter in the X direction. This demonstrates the capability of our method to detect density inhomogeneity in the ribbons.

## III. Summary

In this work we demonstrate the ability of THz imaging to perform non-destructive density measurements in the pharmaceutical industry. Density can be obtained from the change of phase of the transmitted wave for a known sample thickness. A change of density on the samples is translated into a change on the real part of the permittivity, and consequently on a measurable change of phase of the received signal.



**Fig. 4.** Dielectric permittivity versus bulk density for paracetamol patterned ribbons.

### References

[1] R. Dahlbäck, T. Rubaek, M. Persson, and J. Stake, "A System for THz Imaging of Low-Contrast Targets Using the Born Approximation," *IEEE Trans. THz Sci. Technol.*, vol. 2, no. 3, pp. 361–370, Sep. 2012.

[2] N. Souihi, G. Reynolds, P. Tajarobi, H. Wikström, G. Haeffler, M. Josefson and J. Trygg, "Roll compaction process modeling: Transfer between equipment and impact of process parameters", *International Journal of Pharmaceutics*, Vol. 484, pp. 192–206, Apr. 2015.

[3] S. O. Nelson, "Density-permittivity relationships for powdered and granular materials", *IEEE Trans. Instrum. Meas*., Vol. 55, pp. 2033–2040, Oct. 2005.