

Terahertz spectroscopy of a multi-component tablet system to assess the density of simulated roller compacted ribbons

Monwara Hoque¹, Elaine Harrop Stone¹

Xiao Hua Zhou², Mark Sullivan²

¹Merlin Powder Characterisation Ltd, Loughborough, UK

²Advantest America, Inc., Princeton, New Jersey



Introduction

Roller compaction (RC) is a continuous dry granulation process which is fast becoming a method of choice over wet granulation for pharmaceutical tablets. Pressure is applied to a powder feed to densify the powder to create granules with improved flow characteristics and uniformity while still retaining acceptable tensile strength. Typical solid fraction regions for roller compacted granules are 0.5-0.7 and 0.8-0.85 for tablets.

Zinchuk et al. studied simulation of the roller compaction process using a small scale compaction simulator. They were able to show that real and simulated ribbons compacted to the same solid fractions exhibited equivalent tensile strengths.^[1] The interrelations between punch pressure, tensile strength and solid fraction^[2] are shown in Fig. 1.

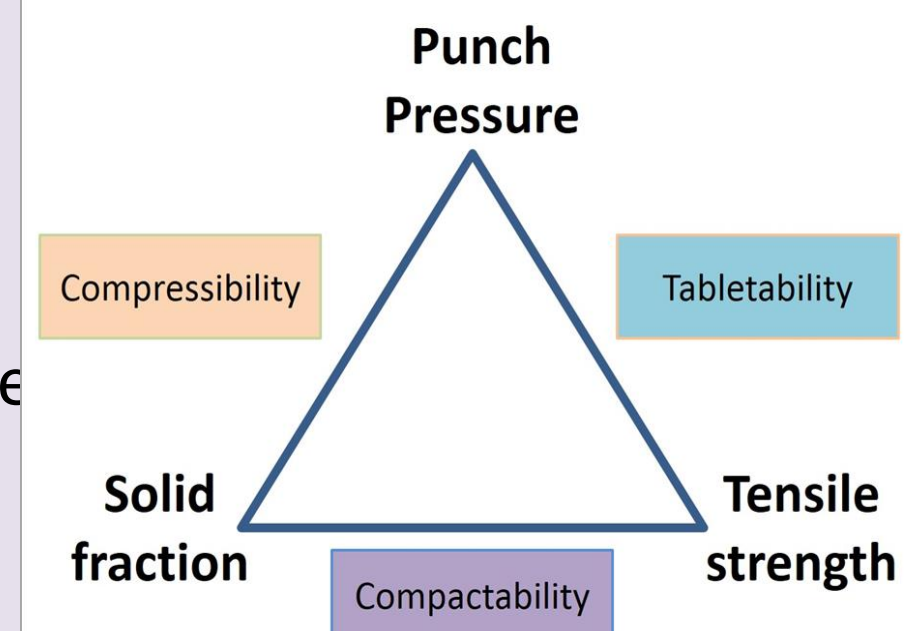


Fig. 1: Powder compaction relationships

In-process monitoring of the solid fraction of intermediate ribbons and final tablets is critical for assuring quality and can provide a more robust means of ensuring consistent product performance^[3]. While custom devices measuring normal stress across the roll surface have been used to predict ribbon density^[4], in-process sensors to directly measure and control the quality of the roller compacted ribbons have been lacking.

However, a recent study has reported that pulsed terahertz (THz) techniques provide a rapid, non-destructive method for measuring solid fraction in RC ribbons^[5].

The purpose of this work is to demonstrate that compaction simulation can be used to calibrate a terahertz analyzer on a multi-component tablet system for rapid, non-destructive in process monitoring of roller compaction and tableting processes.

Materials and Methods

Roller compaction blend composition		
Excipient	Concentration	Manufacturer
Lactose Monohydrate	54.5 % w/w	FlowLac 100 Meggie, Germany
Microcrystalline Cellulose	35 % w/w	Avicel PH102 FMC, Belgium
Dibasic Calcium Phosphate Dihydrate	10 % w/w	Emcompress JRS Pharma, Germany
Magnesium Stearate	0.5 % w/w	Sigma Aldrich, UK

Table 1: Formulation composition for roller compaction blend

Excipients were blended for 10 minutes using a Turbula T2 mixer at 30 rpm. Lubricant was added and blended together for a further 2 minutes. Blend true density was determined using a Helium Pycnometer (AccuPyc II 1340, MicroMeritics).

THz measurements were performed using an Advantest TAS7500 SP spectrometer in transmission mode using measured tablet thickness to calculate refractive index (RI).

Manufacture of ribbons and tablets

Testing was performed using a hydraulic Compaction Simulator (Phoenix Calibration and Services Ltd, Brierley Hill, UK) with 10 mm diameter flat faced punches (Fig. 2).

Simulated Ribbons using RC profile

For the ribbon generation, a double ended sinusoidal compression profile was designed to simulate a roller compactor as described by Zinchuk et al (2004)¹ using the equation: $D=R \sin(\omega t)$, where D = punch displacement, R = roll radius, ω = roll rotation frequency and t = time. The simulation used a roller radius of 50 mm and a roll speed of 4 rpm.

The die was hopper filled with 300 mg of the roller compaction blend and compressed to various thicknesses to produce ribbons of six different solid fractions (typical range 0.5-0.7). Ribbons from three of the simulated solid fractions were milled using a miniature mill (Krupps coffee grinder) and screened through a 500 μ m sieve, providing granules of different solid fractions for tableting (Fig. 3).

Simulated high speed manufacturing profile

For the tableting process, the die was manually filled with 300 mg of the granules and used the same 10 mm diameter flat face punches to compress the tablets. A single ended sine wave profile with an average punch speed of 300 mm/s was used to simulate high speed production conditions with an extended dwell of 10 ms.



Fig. 2: Phoenix compaction simulator

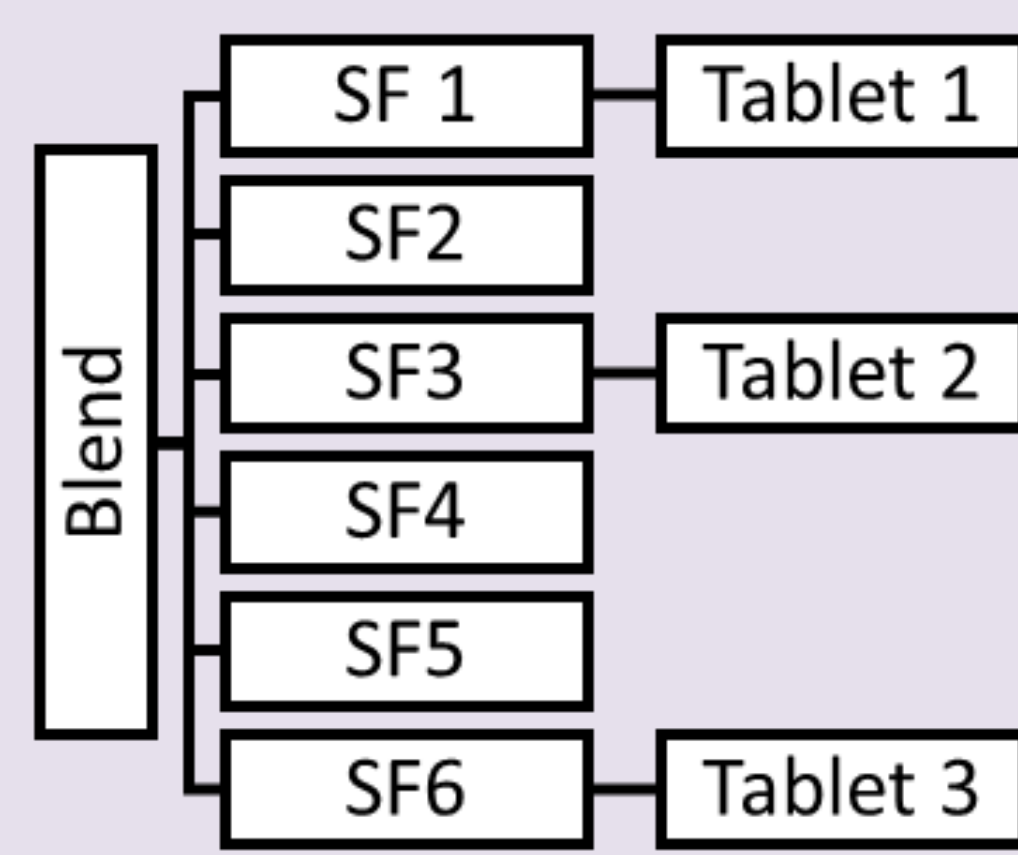


Fig. 3: Solid fractions ribbons and tablets

The compact thickness and diameter were measured and used to calculate the out-of-die volume of the compact. The in-die volume was calculated using the minimum punch separation measurements from the compaction simulator. The compact was weighed and density and solid fraction were calculated. Tensile strength was calculated using equation $\sigma = 2P/\pi Dt$ ^[6]

Tableability, Compressibility & Compactability

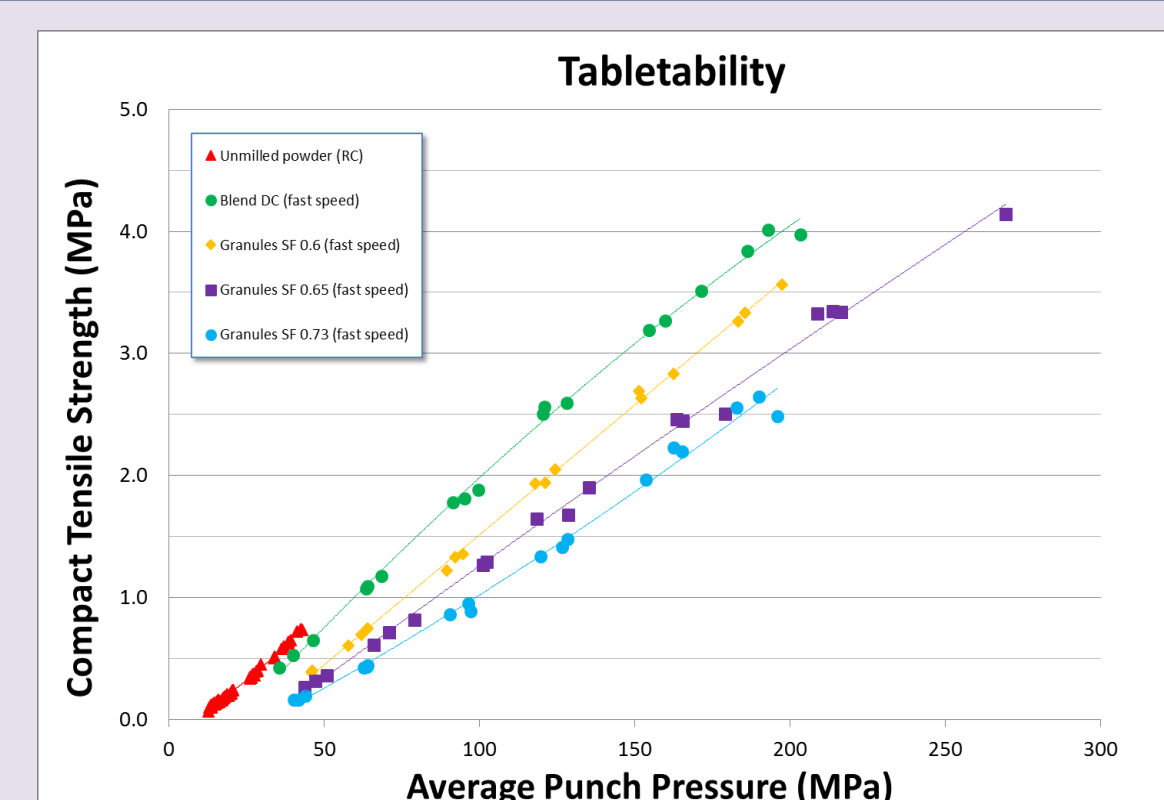


Fig. 4: Tableability plot

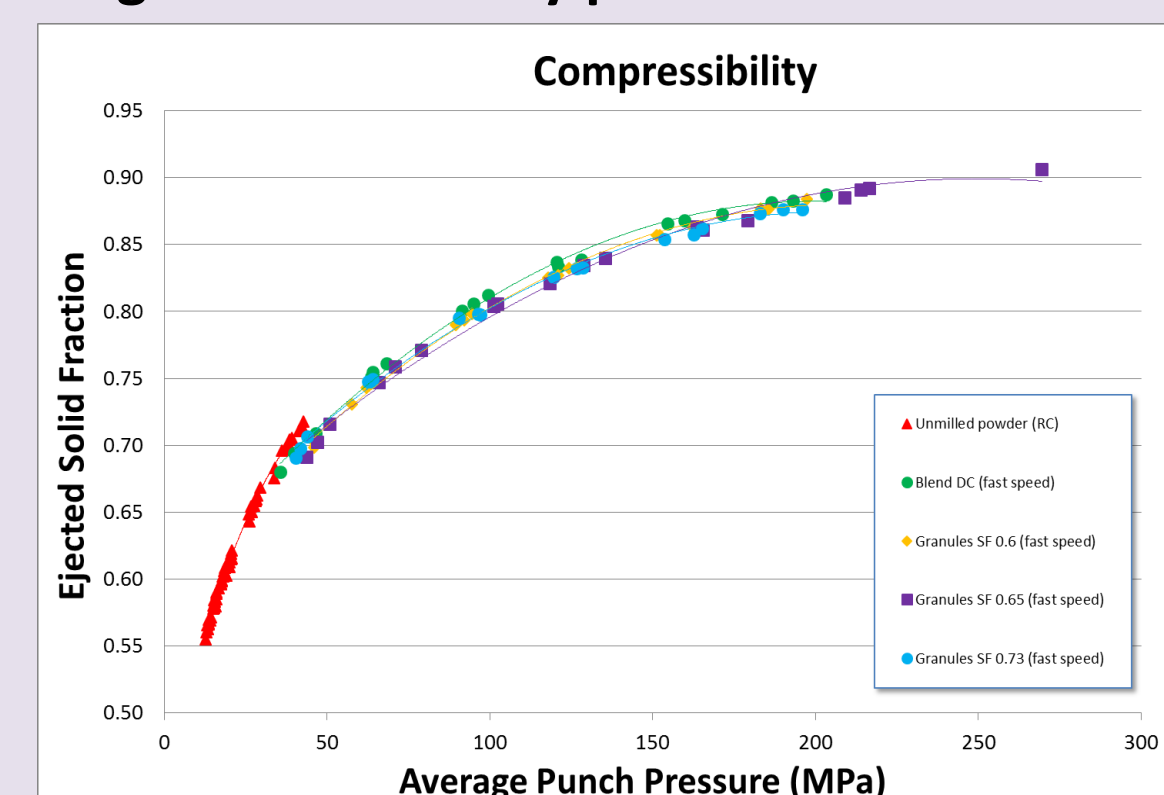


Fig. 5: Compressibility plot

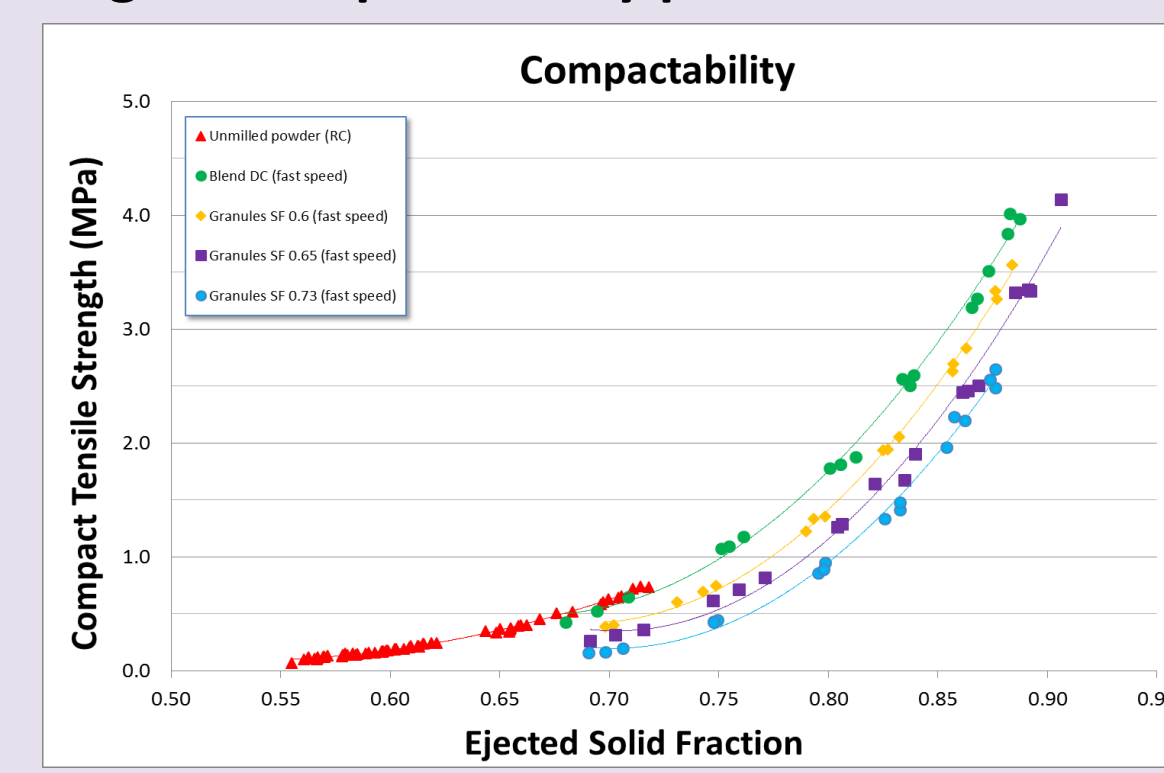


Fig. 6: Compactability plot.

Tableability describes the effectiveness of applied compaction pressure in increasing the compact tensile strength^[2]. Fig. 4 shows simulated ribbons and tablets were produced using the RC profile and high speed manufacturing profile. The DC blend produced compacts with the highest tensile strength at high speeds. Subsequent tablets produced from the RC granules for a given pressure, delivered compacts with lower tensile strength as the solid fraction of the granule increased. This is because some of the compressibility of the material had been used during the roller compaction process.

Compressibility is the ability of the material to undergo volume reduction as a result of applied pressure. It is shown by plotting solid fraction versus pressure. Fig. 5 shows good correlation in the increase of solid fraction of the DC blend and RC granules across the pressure range. The compressibility is similar for the blend and granules.

Compactability is the ability of a powdered material to be transformed into tablets with strength during densification. It reflects the two important effects of applied pressure: tensile strength and solid fraction. Solid fraction of the final tablet cannot be a predictor of tensile strength without knowing the properties of the granule from which it was made as some of the bonding potential is used up in the RC and milling step. Fig. 6 shows as solid fraction increases for the RC granules, the tensile strength of the compacts decrease. At the same solid fraction the DC blend produced the strongest compacts.

Terahertz spectroscopy (THz)

The terahertz RI technique measures the time-of-flight for a pulse of energy passing through a known thickness of the sample. Because it is a measurement of time rather than pulse amplitude, it is inherently a measure of density/porosity and is not affected by mass absorption. Data was obtained using the Advantest TAS7500 Terahertz Spectroscopy System (Fig. 8). The calibration of terahertz RI vs. solid fraction resulted in a high level of linearity and precision in this study (Fig. 9).

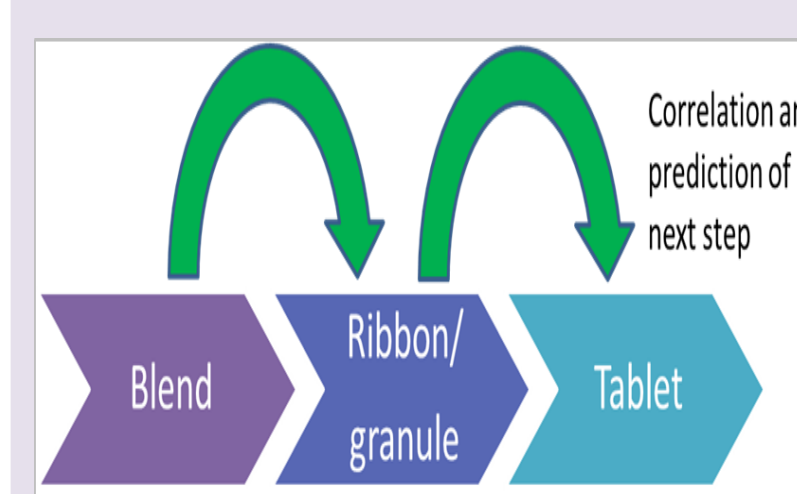


Fig. 7: Calibrated steps using Terahertz spectroscopy



Fig. 8: Advantest TAS7500 Terahertz Spectrometer

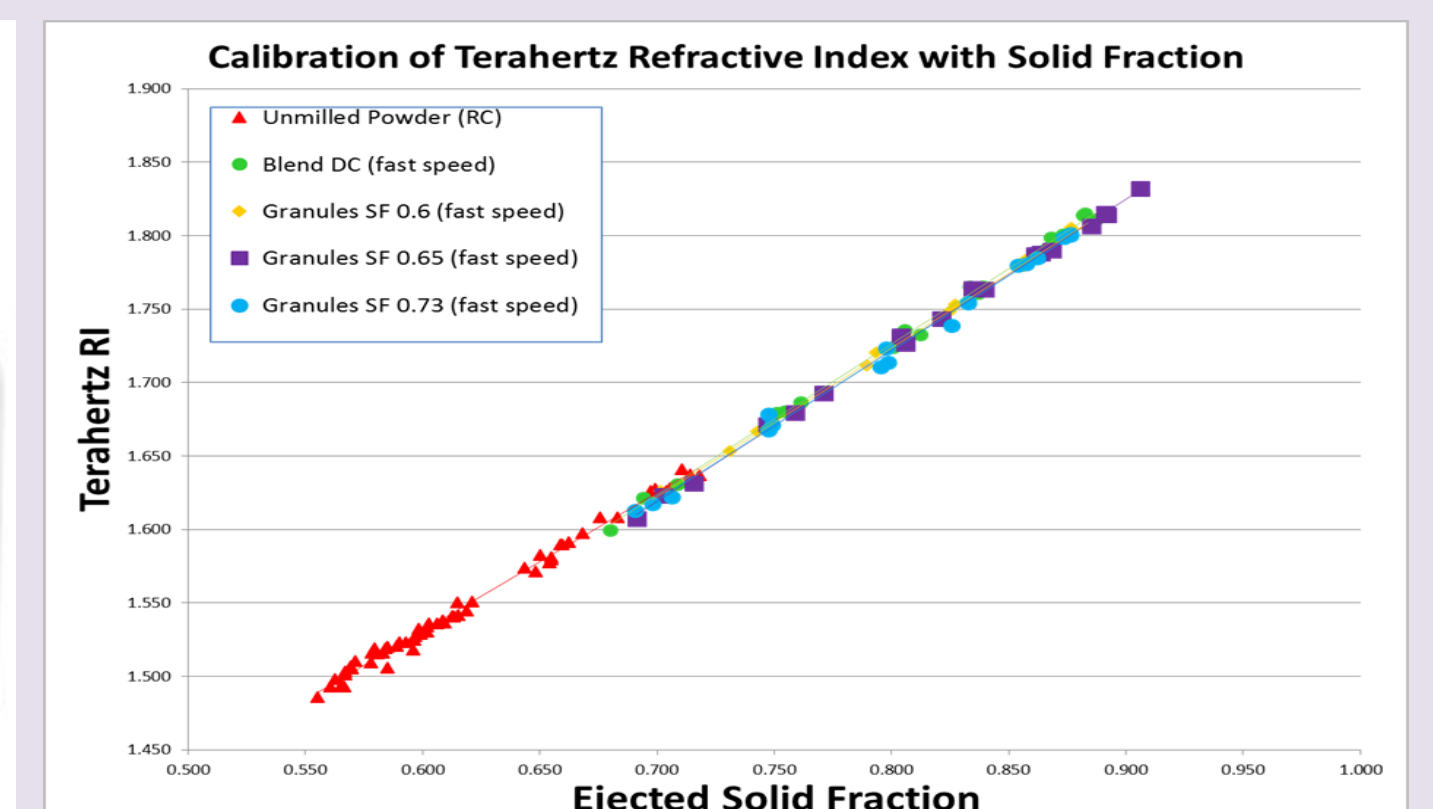


Fig. 9: Terahertz RI correlates with solid fraction

The results show that compacts from the blends and simulated RC granules are capable of producing a good correlation which can be used for calibrating the Terahertz spectrometer for use in a production setting.

It is important to note that for the compaction of RC granules, the solid fractions of both the ribbon intermediate and the tablet are needed to predict tablet tensile strength. Terahertz spectroscopy provides a fast, non-contact measurement of solid fraction of both ribbons and tablets that can be easily adapted for on-line analysis, yielding a comprehensive correlation to tensile strength of the final tableted product.

Conclusions

Solid fraction is a critical quality attribute of ribbon quality and tablet performance but is difficult to measure in production with existing technology. Pulsed terahertz spectroscopy is a fast, non-contact technique for measuring solid fraction in compacts and has the potential to be easily implemented in on-line PAT applications in both roller compaction and tableting. Calibration of the terahertz method can be efficiently and accurately obtained by conducting a small scale piloting study for formulation development using a compaction simulator.

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