tablet analysis

Tablet exam: Using dynamic compaction analysis to ensure successful formulations

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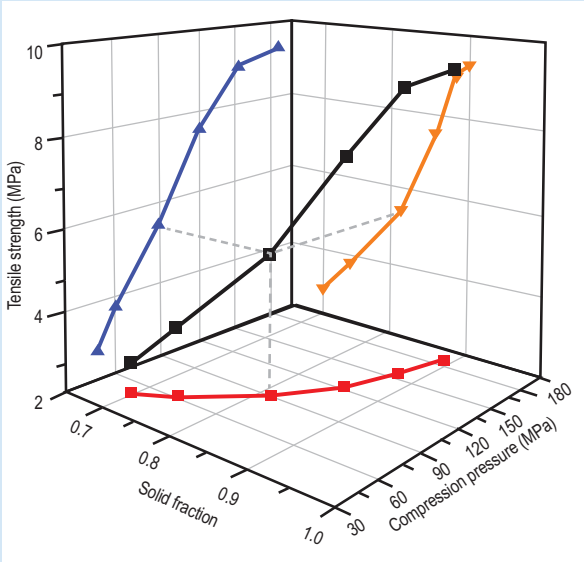
Gamlen Tableting

This article describes a method for performing dynamic powder compaction analysis and a method for measuring the tensile fracture strength of tablets. By combining these two methods, you can better assess the tabletability of pharmaceutical powder formulations. A case study of orally disintegrating mini-tablets illustrates how to use the methods.

Scientists who are tasked with formulating and manufacturing robust yet effective tablets face many challenges. To help formulators overcome these challenges, Amidon and Sun recently proposed a USP monograph, <1062>, that defines the compaction design space (Figure 1) [1].

Figure 1

Three-dimensional compaction design space plot, as proposed by Amidon and Sun in USP draft monograph, "Tablet Compression Characterization <1062>" [1]



Nonetheless, optimizing tablets remains a big challenge for formulators, particularly during the early stages of development, when access to affordable and easy-to-use tools is limited. Specific challenges include identification of critical quality attributes (CQAs), characterization of the suitability and batch-to-batch tolerances of key excipients, accessing API-excipient and excipient-excipient compatibilities, and determining critical process parameters.

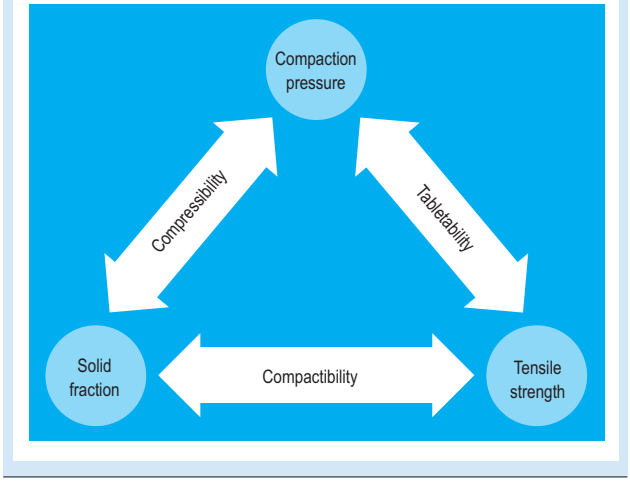
This article highlights a comprehensive tablet exam protocol that combines dynamic powder compaction analysis with tensile fracture stress measurement of the resulting tablet. Together these measurements provide a fast, affordable, and highly predictive measure of the ultimate tabletability of a pharmaceutical powder formulation. They also provide unique real-time insights into the compaction process.

The powder compaction triangle

The CQAs of a powder to be compressed into a tablet are defined by the powder compaction triangle (Figure 2) [2].

Figure 2

The powder compaction triangle



They include but are not limited to:

- Compressibility: The ability of a powder to undergo volume reduction under pressure.

• Compactibility: The ability to yield a compact of adequate deformation resistance when compressed.

• Tabletability: Tablet tensile strength as a function of compaction pressure.

To better understand powder compaction, we've undertaken a dynamic in-die analysis of both the compression event and the tablet dimensions. That enables us to record in real time how a tablet's solid fraction changes as a function of compaction pressure. Next, by combining this information with fracture-stress data from the resulting tablet, we can accurately predict which of the formulation's specific properties needs to change in order to create an optimal tablet. This data also enable us to generate a full profile of the compressibility, compactibility, and tabletability of a single sample.

Furthermore, by entering this information—specific to both excipients and APIs—into a database, formulators can streamline their future efforts and be more prepared to undertake Quality-by-Design (QbD) initiatives. It's even conceivable that an at-line QC operation could use such a database to gain insight into the compression properties of in-process materials via a single-point measurement [3]. An example of how to collect and apply compaction data is discussed below. But first, let's review the principal component of the compaction triangle: tabletability.

A brief review of tabletability

Based on the work of Newton and Fell [4], tabletability is defined as the relationship between compaction pressure and tensile strength. In his pioneering paper of 1972 [5], Newton calculated tablet tensile fracture stress (TTFS) values using this formula:

$$\sigma_t = \frac{2P}{\pi D t}$$

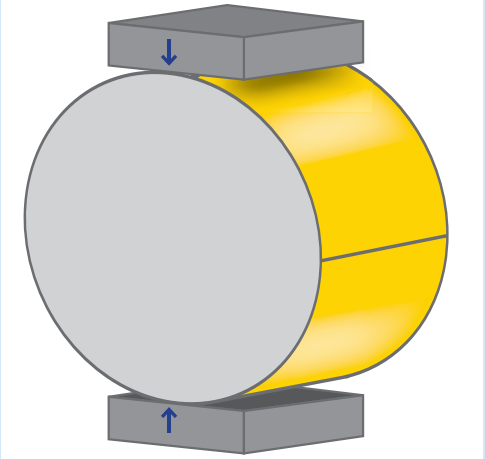
where
σt is the TTFS expressed in megapascals (MPa)
P is the breaking load expressed in newtons (N)
D is the tablet diameter expressed in millimeters (mm), and
t is the tablet thickness expressed in mm.

In practice, the TTFS is easy to measure. Simply apply a diametral load very slowly to a flat-faced tablet and measure the force required to break it (Figure 3). As long as your instrument is sufficiently sensitive, this technique can differentiate easily between small differences in TTFS.

As you would expect, the formulation and/or process with the best tabletability—the material that results in the strongest tablet at a given pressure—is usually the best. That's because the tablet can be made at the lowest compaction pressure, which makes it easier to manufacture. This tablet would also have the lowest solid fraction (highest porosity) of the formulations studied, which typically corresponds to the best dissolution behavior. In fact, measuring tabletability is recognized as a simple, highly sensitive, and effective way to characterize and compare the compaction properties of component materials and powder formulations. Plus, the measurements are independent of both tablet size and shape. Because tabletability accounts for the effects of the formulation and the process, it offers formulators a practical and valuable approach [3].

FIGURE 3

Diametral measurement of TTFS



Assessing the compaction behavior of orally dispersible mini-tablets

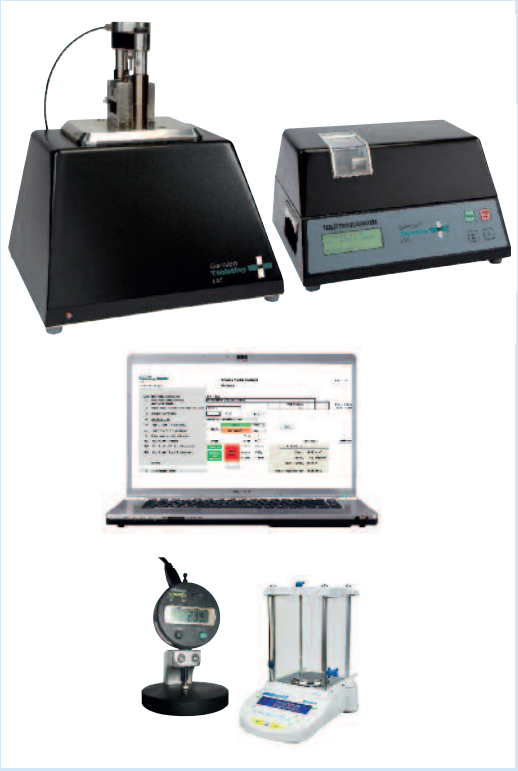
There are several good reasons for improving how we assess individual materials before defining the compaction design space of a formulation. The best reason: It would minimize trial and error—thus saving valuable development time—by applying knowledge-based principles instead of relying on empirical observations and experience. This is particularly valuable when characterizing excipients, which are subject to batch-to-batch variation. Many excipient variations are supplier-dependent and may be difficult or impossible to predict or control. Thus, implementing a protocol to evaluate the compaction properties of incoming excipients can help you screen new batches before you incorporate them into a new tablet formulation.

To illustrate how such tests can improve our assessment of tablets, we studied the effect of compaction pressure on the CQAs of orally dispersible mini-tablets (ODMTs). The study used a PCA-500 powder compaction analyzer (Gamlen Tableting, Nottingham, UK) and a TTA tablet tensile analyzer (Gamlen Tableting). See Figure 4. The ODMTs were prepared using SmartEx (Shin Etsu, Tokyo, Japan), a coprocessed excipient that comprises low-substituted hydroxyproyl cellulose as the disintegrant, mannitol as the filler, and polyvinyl acetate as the binder. ODMTs are designed to disintegrate without water inside the buccal cavity. They are particularly useful for dosing pediatric and geriatric patients who have difficulty swallowing. The dissolution profile of an API delivered via ODMTs is easy to control by varying

how many mini-tablets are filled into a capsule.

FIGURE 4

Powder compaction analyzer and tablet tensile analyzer used to assess tabletability



The compaction analyzer. The powder compaction analyzer used in this study produces tablets 2 to 15 mm in diameter and uses a computer that precisely controls and records both force and punch position in real time. This analyzer was recently upgraded to include a rotating die plate that enables it to automatically measure and record tablet detachment (take-off) force and tablet ejection force. It also allows you to program a pre-set dwell or "hold" time after maximum compression is obtained. The hold time can last 90 milliseconds (ms) to 1 minute. Because the analyzer records both force and punch position in real time, it can also record in-die dynamic changes in real-time using Heckel and Kawakita parameters at all compression forces—not simply the maximum force—while simultaneously tracking real-time changes in tablet volume. This dynamic measurement capability offers a new avenue for exploring and understanding powder compaction.

The tensile analyzer. The tensile tablet analyzer used in this study automatically records out-of-die weight, thickness, and diameter of tablets made using the powder compaction analyzer. It then measures the TTFS.

The CQAs of an ODMT require that it be measured under controlled compaction pressure. In this case, the CQAs were solid fraction, friability, disintegration, and TTFS. (Dissolution test performance is not a CQA of ODMTs.)

The methodology for measuring these four CQAs included

- Blending the formulation with a lubricant (1 percent magnesium stearate) for 3 minutes using a Turbula mixer (WAB, Muttenz, Switzerland).
- Weighing out the resulting mixture and making tablets 3 mm in diameter, each weighing 25 milligrams (mg). The compaction, detachment, and ejection forces were recorded.
- Testing friability.
- Comparing the disintegration times of the compacts with respect to the different compaction forces.
- Characterizing the compacts, which included measuring their weight, thickness, diameter, and TTFS.

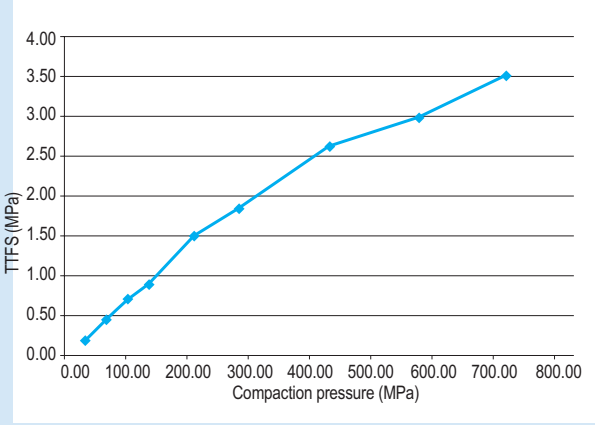
Solid fraction. Measuring the solid fraction is useful for comparing formulations with significantly different compositions, and for a fair comparison, the formulations should be compared at similar solid fractions. The comparison requires accurately measuring the true density of the formulation. This is not always available, so in many cases the optimization is based around the use of compaction pressure measurements, as discussed in this article.

The relationship of the TTFS to compaction pressure is fundamental and arises from the characteristics of a formulation or material. This relationship has been shown to extrapolate to compaction behavior during production. Thus, based on the results of a simple laboratory test, we can make reliable predictions about production behavior.

Figure 5 shows the effect of compaction pressure on the TTFS of the ODMTs. This is generally a linear relationship until high solid fractions are reached and thus provides a simple and objective way to compare tablet formulations and processes.

FIGURE 5

TTFS versus compaction pressure for ODMTs made from a coprocessed excipient



Friability test. Seven ODMTs made at four compaction pressures (139, 208, 278, and 345 MPa) were tested in a friabilator (Erweka, Heusenstamm, Germany) set for 100 revolutions (25 rpm for 4 minutes). Table 1 and Figure 6 show the results.

Achieving friability limits can be difficult when formu-

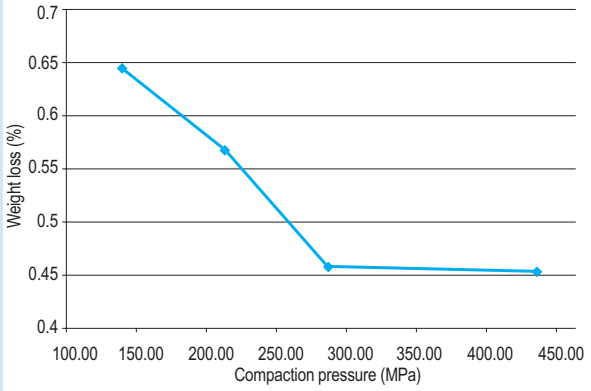
Table 1

Friability of ODMTs

Compaction pressure (MPa)	Initial weight (mg, average of 7 tablets)	Final weight (mg, average of 7 tablets)	Weight loss (mg)	Weight loss (%)
139	175.10	173.97	1.13	0.645
208	175.90	174.90	1.00	0.569
278	174.70	173.90	0.80	0.458
345	176.50	175.70	0.80	0.453

Figure 6

Percentage weight loss from ODMTs after friability testing



lating ODMTs because tablet strength is directly related to the compaction force used. As a result, an accurate quantity of disintegrant must be added to promote rapid disintegration in the buccal cavity, where there is little moisture. The range of acceptable friability was set between 0.1 and 0.9 percent weight loss based on our experience with orally disintegrating products. All the ODMTs made at pressures ranging between 130 and 350 MPa met the friability requirement. This pressure range was selected because it corresponded to the most favorable region from the plots of TTFS and compaction pressure shown in Figure 5.

Disintegration test. The disintegration test was performed using a PZT-S tester (PharmaTest, Hainburg, Germany). The tablets were placed in vials, and the disintegration bath was filled with 800 milliliters of water. The temperature was regulated using two thermometers to ensure that the tablets were tested at the optimal temperature of 37° to 38°C.

By definition, orally disintegrating tablets must disintegrate within 30 seconds. For this test, three tablets made at each of the eight compaction forces (24 tablets total) were tested and the results averaged. See Table 2. As shown in Figure 7, the ODMTs made at compaction pressures exceeding 278 MPa did not meet the 30-second standard.

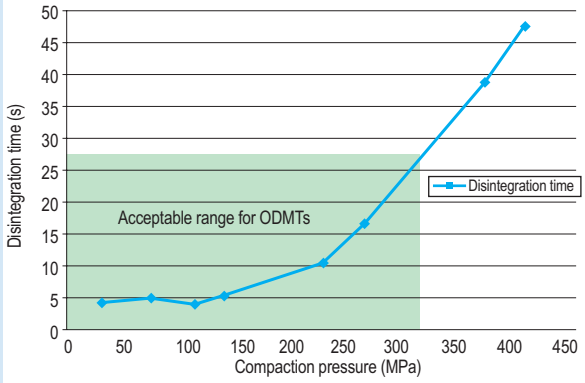
Table 2

Disintegration time of ODMTs

Compaction pressure (MPa)	Disintegration times of 3 tablets (s)	Average disintegration time (s)
35	4, 4, 5	4.33
69	5, 5, 5	5
104	5, 5, 4	4.67
139	5, 6, 5	5.33
208	9, 11, 11	10.33
278	17, 17, 16	16.67
346	38, 39, 39	38.67
416	47, 48, 48	47.67

Figure 7

Disintegration time plot



TTFS. The TTFS of the ODMTs was measured using the tablet tensile analyzer described above. It includes multiple interconnected components, including a top-loading balance, digital micrometer, and a sensitive load cell. The TTFS system automatically measures and records the final weight, thickness, and diameter of each tablet before measuring tensile fracture stress. Figure 8 shows the TTFS measurements for each tablet made at 75-, 150-, and 250-kilogram (kg) loads. Note the difference in results when the analyzer used a 10-kg load cell instead of a 500-kg load cell, which is less sensitive. In operation, the analyzer measures tablet diameter first, detects the force required to break the tablet, and then immediately stops measuring and returns to the start position. Because this method records the tablet's force-displacement profile during fracture and records the load at the point of fracture, it gives more accurate results than less sensitive analyzers that operate at higher speed. They tend to overstate the fracture load and provide no information about the force-displacement profile.

As shown earlier in Figure 5, the ODMTs must be made at a compaction pressure of approximately 1 MPa in order to meet the minimum hardness requirement. But identifying the optimal compaction pressure requires

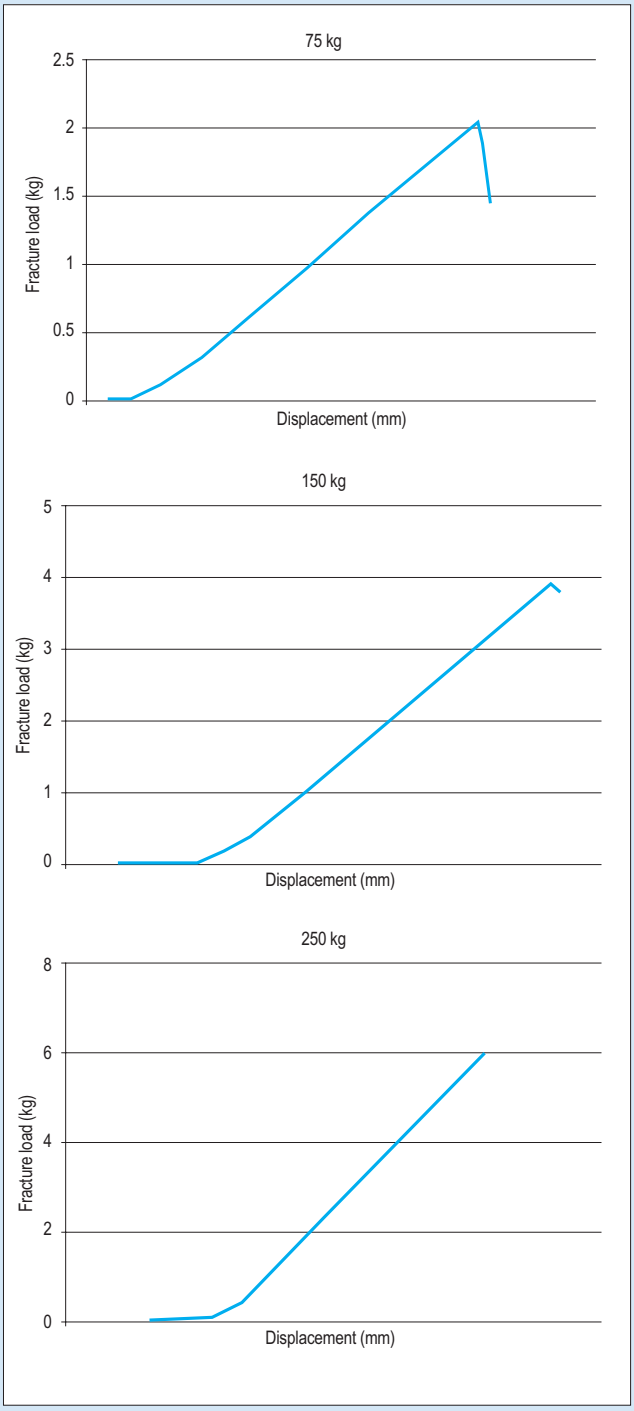
adding the data collected from the friability and disintegration tests. In this case, the coprocessed excipient yielded tablets of acceptable tensile strength over a wide range of compaction forces. Most of these tablets disintegrated within the required 30 seconds, but those made at 346 and 416 MPa did not. Considering that people prefer ODMTs to disintegrate quickly, the optimal compaction pressure for these 3-mm flat-faced tablets is between 139 and 208 MPa. In that range, hardness is between 1 and 1.5 MPa; friability weight loss is between 0.57 and 0.65 percent; and disintegration time is between 5 and 10 seconds. Although not shown here, the ejection and detachment forces measured by the powder compaction analyzer were within acceptable limits.

Other work

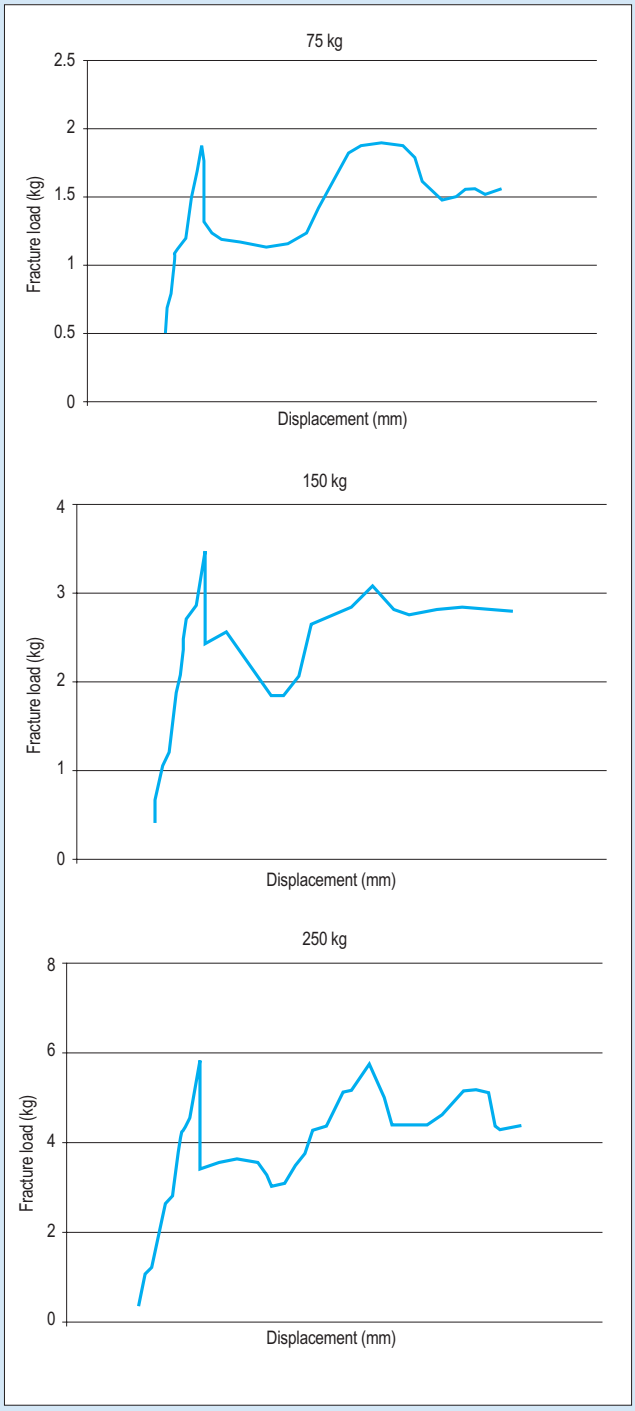
The most exciting data we are currently evaluating relates to the in-die dynamics of the compaction process

FIGURE 8

TTFS measurements made using 10-kg load cell versus 500-kg load cell



a. 10-kg load cell



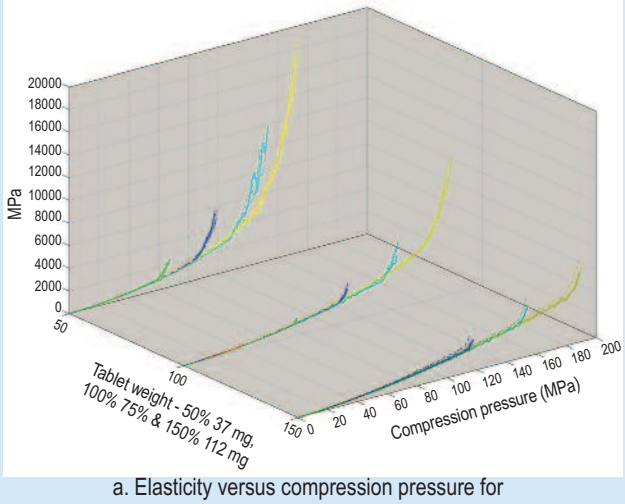
b. 500-kg load cell

itself. Using the powder compaction analyzer, we have taken real-time measurements of both the punch position and the punch force. That enables us to analyze continuous force-displacement data to understand the dynamics of compaction in real time. This analysis includes a dynamic profile of both yield stress (a measure of plasticity) and Young's modulus (a measure of elasticity) of the powder bed during compaction. Figure 9 illustrates dynamic compaction profiles for three different tablet weights of Avicel PH102 microcrystalline cellulose (FMC, Philadelphia, PA).

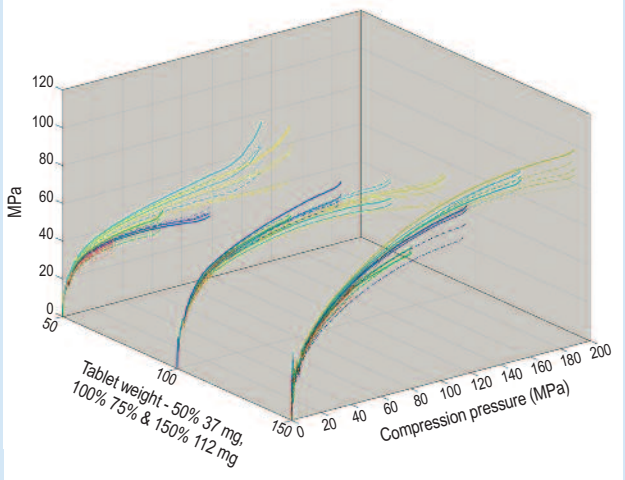
Yield stress is tablet-size dependent and the yield stress profiles shown here confirm that. What's more notable is that the elasticity profiles are independent of tablet size. We're evaluating this new work to understand the significance of this novel in-die dynamic compaction analysis and to identify how the information can be directly applied to improve formulation development.

FIGURE 9

Three-dimensional dynamic compaction profiles of elasticity and plasticity



a. Elasticity versus compression pressure for microcrystalline cellulose at three tablet weights



b. Plasticty versus compression pressure for microcrystalline cellulose at three tablet weights

Future applications

Dynamic powder compaction analysis can play a key role in developing tablet formulations. To get the most benefit, we should routinely characterize the compaction behavior of individual excipients, APIs, and formulations very early in development. By so doing, we can apply the data to new mechanisms of feedback and/or feedforward control systems that determine whether batches meet minimum standards. Better yet, these control systems could ensure the optimal combination and concentration of excipients and API in our blends.

Dynamic in-die compaction measurements may also help us understand the complexity of tablet formulations. It's even conceivable that an at-line benchtop tablet exam will be able to use an historical database of material-specific compaction data to simplify in-process decisions using a single-point compaction measurement. *T&C*

References

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