

A critical step

Tablet manufacturing poses many challenges and the development process of a tablet form is a critical step that requires the correct tools and equipment. In this article, Robert Sedlock, director of Technical Training and Development for Natoli Engineering Company, will discuss the three phases of the tablet development process: Pre-formulation, formulation, and scale-up, as well as how to use the machines and tools available to provide science supported decisions.



Tablet manufacturing poses many challenges but is still the preferred pharmaceutical dosage form. Compressing a block of particles into a single compact is a science that must be understood to ensure a successful manufacturing process.

For consumers, tablets are a simple and convenient dosage form and if developed properly tablet manufacturing rates are higher than any other dosage form available.

The tablet development process is a critical step that requires the correct tools and equipment to minimise the challenges through scale up and in the manufacturing environment. A quality by design (QbD) approach requires careful characterisation and an understanding of the properties and limitations of the product and process.

From a tableting standpoint, it is important to complete the material science work upfront. This applies to API's, excipients, diluents, binders and formulation mixtures. Among the most significant challenges in early tablet development are the high costs and limited amounts of material available for laboratory experiments and process scale up. Material sparing tools for powder characterisation such as single-station tablet presses, compaction simulators and emulators are essential to cost effective tablet development.

Pre-formulation

At this stage, the mechanical properties of the API are characterised. Commonly, API's do not have sufficient bonding properties to

form a robust compact, requiring appropriate excipients during the formulation process. Some properties of note include the deformation characteristics, compactibility, ejection force levels and sticking potential.

Single-station tablet presses, compaction simulators and compaction emulators are all very effective tools to help characterise mechanical properties of your API. These machines can provide compression data from one single tablet and only require milligrams of material. Additionally, a linear displacement sensor can be easily installed allowing real time in-die thickness measurements — enabling recording of the punch displacement along with the compression force profile associated with the compaction event. This can provide an understanding of:

- The consolidation of the particles during compression.
- When plasticity occurs.
- Inter-particulate bonding.
- The elastic energy or work put into the tablet and remaining work after the decompression event.

Other valuable measurements include the upper and lower compression force, ejection force, residual and peak radial die wall force and take off/punch adherence force.

Single-station tablet presses (figure 1) are a cost-effective way of recording the above measurements but they do not simulate the compression event of a high-speed production tablet press. Materials that undergo compression at slow rates have more time for the particle consolidation process, increased dwell time or the time under maximum force and relaxation time during the decompression event. This may result in a stronger compact as compared to the

manufacturing process where the tablet presses are running at high velocities and have low dwell times, which can result in insufficient tablet strength, capping or lamination.



Figure 1) NP-RD10A single-station tablet press.

Furthermore, most single-station tablet presses are designed for single ended compression — the upper punch applies and the lower punch receives the force through the powder bed. A typical manufacturing tablet press is designed with an upper and lower compression roller and both punches travel in the die to compress the tablet. Despite this limitation, a single ended compression cycle can provide useful information if both the upper and lower punch forces are recorded.

A compaction simulator is a sophisticated single-station tablet press designed to mimic a double ended compression cycle of a rotary press at high velocities. These machines are typically hydraulically or electrically driven and fully instrumented including punch displacement profiles.

A compaction emulator is also a highly technological press designed to mimic a double ended compression cycle of a rotary press at high velocities. A compaction emulator

is mechanically driven and leverages the design of a traditional rotary press where the upper and lower punches are forced between a set of compression rollers (figure 2).



Fig. 2) Presster compaction emulator.

The punch type, head profile and compression rollers are easily replaced to replicate the production tablet machine that will potentially be used during the manufacturing process. Furthermore, a compaction emulator is designed with a linear track allowing the punches and die to travel through a fill track, dosing stage, compression rollers and a user set ejection angle.

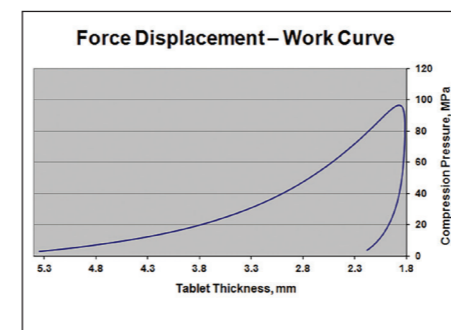


Figure 3) Single-station data — work curve

A work curve or force displacement curve measures the real-time tablet thickness during a single compression event (figure 3). As the compression force increases the tablet thickness decreases and the area under the curve represents the amount of work/energy remaining in the tablet. This information also provides the elastic recovery of the material. In the example given, the elastic recovery is 20.5%.

The Heckel plot provides a linear relationship between the relative porosity of a powder and the applied compaction pressure (figure 4).

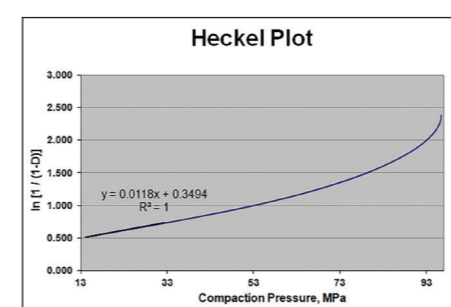


Figure 4) Single-station data — Heckel plot.

The slope of the linear regression is the Heckel constant — the minimum compaction pressure required to cause deformation of the material under compression. In this example, the yield pressure or the Heckel constant is 28 MPa, which is a third of the inverse of the slope, where the slope is 0.0118x.

Formulation

Based on the API properties the excipients can be chosen to provide the necessary deformation properties to provide a robust tablet. At this stage compaction studies can be performed with formulation variants while simulating production tablet press rates and dwell times. From a mechanical standpoint the excipient choices should be made to aid in the powder flow, provide sufficient tablet strength, provide a smooth ejection and take off process with minimal forces. Instrumented benchtop rotary tablet presses are common machines used at this stage. But when bulk quantities of materials are limited single-station tablet presses are still a valuable tool for screening and evaluating formulation compositions. Figures 5, 6 & 7 are examples of compaction studies performed during the formulation process.

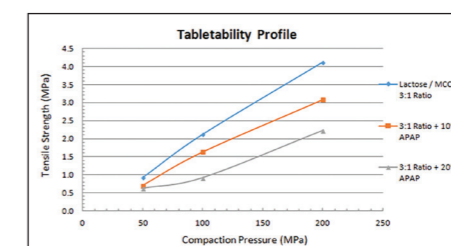


Figure 5) Tensile strength versus compaction pressure.

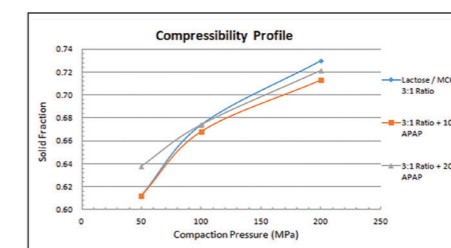


Figure 6) Solid fraction versus compaction pressure.

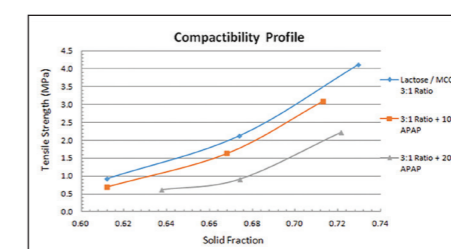


Figure 7) Tensile strength versus solid fraction.

The tableting profile depicts the tablet tensile strength as a function of the applied compaction pressure. This profile is normalised for the punch tip face area and tablet geometry allowing for a true comparison of the formulation robustness independent of tablet size. The example above compares ratios of lactose and microcrystalline cellulose with added acetaminophen (APAP). The added APAP decreases the tablet strength and requires a higher compaction pressure to achieve a desired tablet tensile strength.

This study can be performed on a single-station press but more valuable if performed on a compaction simulator/emulator at the velocities and dwell times of a production tablet press speed.

The compressibility profile depicts the tablet solid fraction as a function of the compaction pressure. The solid fraction is a ratio of the tablet density over the powder true density where the true density can be measured from a helium pycnometer. The tablet porosity is one — solid fraction and this provides valuable data that will influence the disintegration.

The compactibility profile depicts the tablet tensile strength as a function of the tablet solid fraction. This allows the scientist to evaluate the tablet strength as related to the solid fraction and disintegration potential. The tabletability and compactibility profiles are influenced by the speed of the compaction event where the compactibility profile is not speed dependent and can be generated on a slow single-station tablet press while generating valuable information that will transfer to larger scale.

Scale up

At this stage, manufacturing variables can be evaluated on a small scale. Longer production runs can be tested to address any issues found at this level. The effects of processing variables, excipient suppliers, changes in particle size and manufacturing conditions can be evaluated. During this process a pilot scale rotary tablet press is suitable to provide the longer tableting runs where friction and heat play a role and allows the scientist to identify any tablet quality issues. A compaction simulator or emulator is designed to mimic a high speed rotary tablet press and this tool can provide insight in what to expect but it doesn't simulate the continuous movement of multiple punches throughout a series of cam tracks on a rotary turret.

Load cell transducer design, data acquisition performance and calibration techniques are critical aspects that make up a quality instrumentation software system. Load cells can measure compression, tension and shear with a typical error of less than 0.1%. The data acquisition system must be designed to handle data capture rates up to 100 kHz in order to measure data at high tableting speeds typically occurring in 1 to 100 milliseconds. Calibration techniques are also very important to ensure the accuracy of your data. When measuring in-die thickness during the compaction event the linear displacement sensors need to compensate for the machine compliance or deformation. Since tableting machines are not perfectly rigid a calibration should be performed to correct this error.

With the many challenges found in the tableting process a clear understanding of your materials and processes is vital. Material science is of fundamental importance in formulating a robust tablet that is scalable to the manufacturing environment. With the high costs of API's and bulk powders, material sparing systems such as single-station tablet presses, compaction simulators and emulators are of great value.