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 Sealock, 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.

T ablet 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 understanding of the properties and limitations of the product and process.

From a tabletting standpoint, it is important to complete the material science work upfront. This applies to APIs, excipients, diluents, and binder formulations. 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 sourcing for powders characterisation such as single-station tablet presses, compaction simulators and simulators are essential to cost effective tablet development.

Pre-formulation

At this stage, the mechanical properties of the API are characterised. Commonly, APIs 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, compressibility, elasticity, force levels and sticking potential.

Single-station tablet presses, compaction simulators and compaction simulators 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 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-particle 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 residual 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 multicompartment strength, capping or ejection angle.

Furthermore, most single-station tablet presses are designed for angled ejection compact — the upper punch applies force 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 the limitations, 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 hydrostatically or electrically driven and fully instrumented including punch displacement profiles.

A compaction simulator is also a highly technological press designed to mimic a double ended compression cycle of a rotary press at high velocities. A compaction simulator is mechanically driven and leverages the design of a traditional rotary press where the upper and lower punches are forced against a set of compression rollers (figure 2). 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 simulator is designed with a linear track allowing the punches and die to travel through a full track, closing stage, compression rollers and a user set ejection angle.

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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 pressure or the Heckel constant is 28 MPa, which is a third of the inverse of the slope, where the slope = 0.0116.

Load cell transmitter design, data acquisition performance and calibration techniques are critical aspects that make up a quality instrumentation software package. Real-time data capture is a measure compression, tension and shear with a precision of within ±1%. The data acquisition system must be designed to handle data capture rates up to 100 kHz in order to measure data in high tableting speeds, typically occurring in a traditional rotary press at 1000 to 12000 strokes per minute. 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 be calibrated for the machine compliance or deformation. Since tabletting machines are not perfectly rigid a calibration should be performed to correct this error.

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 force. Instrumented benchtop rotary tablet presses are commonly 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.

The tablettability profile depicts the tablet tensile strength as a function of the tablet solid fraction. This study can be performed on a single-station press but more valuable if performed on a compaction simulator/emulator at the same single-station press rates and dwell times as a production tablet press speed.

The compressibility profile depicts the tablet solid fraction as a function of the compression process. 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 provides valuable data that will influence the disintegration.

The compressibility 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 tablettability and compressibility profiles are influenced by the speed and the compression event where the tabletting process occurs. The compressibility profile is not speed dependent and can be generated on a single-station tablet press while generating valuable information that will transfer to larger scale.

Scalup

At this stage, manufacturing variables can be evaluated on a small scale. Single-station tablet presses and runs can be tested to address any issues found at this level. The effects of processing variables, excipient changes in particle size and manufacturing conditions can be evaluated. During this process a pilot scale rotary tablet press is suitable to provide the larger tabletting 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 the tool can provide insight into what to expect but doesn’t emulate the continuous movement of multiple punches throughout a tonne of core tracks on a rotary turret.

Fig. 9) Single-station data — Heckel plot.

The Heckel plot provides a linear relationship between the relative porosity of a powder and the applied compaction pressure (figure 4). 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 pressure or the Heckel constant is 28 MPa, which is a third of the inverse of the slope, where the slope = 0.0116.

The tabletability profile depicts the tablet tensile strength as a function of the applied compaction pressure. The slope is normalised for the punch tip face area and is designed to mimic a double ended compression cycle of a rotary press at high velocities and high compression pressures. This profile is normalised for the punch tip face area and is designed to mimic a double ended compression cycle of a rotary press at high velocities and high compression pressures. The example above compares ratios of lactose and microcrystalline cellulose with added starchmethyl (APM). The added APM decreases the tablet strength and requires a higher compaction pressure to achieve a desired tablet tensile strength.

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