This article discusses the advantages and disadvantages of different methods for determining the endpoint in a high-shear mixer granulation process and highlights the high-precision direct torque measurement technique.

While fluid-bed granulation is increasing in popularity, high-shear mixer (HSM) granulation remains the most preferred wet granulation method for tablet compression and capsule filling formulations. This method is well established and achieves high-quality granules, but accurately identifying the granulation endpoint is critical for the compression of good tablets and can be a major challenge.
Although technological advances have made a considerable impact on many industries, pharmaceutical operations, such as the granulation step in tableting, have often remained conventional. Pharmaceutical manufacturers employ an array of methods to determine the granulation endpoint, including wet mixing duration, power consumption, calculated torque, reaction torque, torque rheometer, acoustic emission, near-infrared (NIR) spectroscopy, and focused beam reflectance measurement (FBRM).

More difficult than detecting the endpoint of granulation is achieving reproducible endpoints by controlling a range of process variables. For a given set of processing parameter values, the granulation endpoint is determined by measuring the strength, rheological properties such as density, and physical properties such as mean particle size distribution of the granules. This requires an endpoint measurement technique that can provide accurate and reproducible results, taking into account changes in processing parameters, such as mixer geometry, blade speed, batch size, and the amount and method of binder addition.

It is also important to consider the different phases of HSM granulation when determining the granulation endpoint. The HSM process follows three principle phases: dry mixing, spraying or binder addition, and wet mixing. The wet mixing phase has the greatest impact on the endpoint, but the binder addition phase and the method of binder addition also play important roles in granule formation, including granule nucleation, densification, and growth. Hence, predicting the granulation endpoint requires consideration of the binder addition phase as well as the wet mixing phase.

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However, these methods are not exact, and the readings they provide may fluctuate. In contrast, direct torque measurement provides more accurate endpoint detection and fewer reading fluctuations, making it a reliable option for overcoming FDA scrutiny of endpoint determination in HSM granulation processes. Before discussing how direct torque measurement works, however, it’s important to understand the challenges involved and endpoint determination methods currently in use.

**Challenges of endpoint determination in HSM granulation**

The endpoint of a granulation process is the time at which the process forms granules with desirable tableting properties, including strength, bulk density, particle size distribution, and flowability. Over the years, researchers have devised various ways of predicting the results of HSM granulation processes. Simultaneously, granulation equipment manufacturers have improved their machines to provide more reliable results.

Despite these efforts, HSM granulation relies heavily on empirical methods to determine its endpoint.

Because precise endpoint determination is so challenging, most formulations are either under- or over-granulated, leading to a range of problems during downstream processes. Operators still often follow a traditional hand test to check granules, which is highly subjective and can lead to extreme inaccuracies. As a result, the FDA has insisted that manufacturers establish a precise method for determining the granulation endpoint.

**Current methods for determining the endpoint in HSM granulation**

**Wet mixing duration.** One of the oldest methods for endpoint determination is based on the duration of the wet mixing phase, which follows the binder addition phase. The limitation of this method is that it may lead to inaccurate results if the properties of the starting materials vary due to a supplier change or some other circumstance. Also, manually adding binder can introduce errors in addition time and binder quantity that may cause variations in the final granulation lot.

**Power consumption.** Another popular endpoint determination method is based on measuring the power consumed by the mixer motor (in amperes). This is a cost-effective method, and the results obtained can be correlated to granule growth. A change in the consistency of the powder mixture increases the resistance on the granulator blades, which in turn, affects the motor’s power consumption. This method has certain limitations. The readings are affected by various factors such as the formulation, equipment type, and process variables, as well as by the amount of wear and tear on components such as the impeller motor, bearing, and gear box. A major drawback of the power consumption method is that the load is measured on the motor rather than on the impeller where the process is conducted. These measurement readings fluctuate over time and depending on the condition of the motor, regardless of the load.

**Calculated torque.** Another means of endpoint determination is to use the motor current to calculate the torque on the mixer’s impeller. However, HSMs usually have induction motors that use an alternating current. This causes fluctuations in measurement readings and poses limitations. The basis of evaluation is the measured current, which is then converted to calculated
to the shaft, the shaft material twists or "stretches" a very small amount in a direction 45 degrees to the axis. Torque transducers measure changes in the shaft stretching to calculate the torque. This measurement is conducted using strain gauges bonded to the shaft, which measure the strain induced in the shaft by the applied torque or force.

**Torque rheometer.** A torque rheometer provides an offline measurement of the torque required to rotate the mixer blades and can be used to assess the rheological properties of wet granules. The disadvantage of this method is its offline measurement.

**Acoustic emission.** The acoustic emission method uses piezo-electric acoustic emission sensors to determine the granulation endpoint. The granulation process indicators obtained with an acoustic transducer can be used to monitor changes in particle size, flow, and compression properties. It is a non-invasive, sensitive technique but is still relatively expensive.

**Near-Infrared (NIR) spectroscopy.** NIR sensors can be used to determine the moisture content during granulation, but this method does not accurately determine the endpoint of the process.

**Focused beam reflectance measurement (FBRM).** FBRM is a particle size determination technique that uses a laser beam focused in the vicinity of a sapphire window of a probe to determine the chord length distribution (CLD) of the particles. The CLD is a measure of the particles' size, shape and concentration and can be recalculated to represent either the number of particles or the volume-weighted particle size distribution. In many cases, CLD measurements are adequate to monitor dynamic changes in process parameters related to particle size and shape, concentration, and rheology, but the method is expensive.

## Direct torque measurement

Direct torque measurement provides the most accurate, state-of-the-art process control available by measuring the impeller torque in newton meters in real time using a device mounted onto the impeller drive shaft. In comparison to standard torque measurement techniques, which calculate a theoretical impeller torque value based on the impeller drive's current consumption, this technique can eliminate all factors that may influence current consumption, including wear and tear of bearings and gears, oil viscosity, and temperature fluctuations.

Torque sensors use strain gauges that are applied to rotating parts. This can be accomplished using rings, wireless telemetry, or rotary transformers. Figure 1 shows the arrangement of a direct torque measurement device on an impeller hub.

The underlying principle of direct torque measurement is based on measuring the force being used to turn the impeller shaft. When a force or torque is applied to the shaft, the shaft material twists or "stretches" a very small amount in a direction 45 degrees to the axis. Torque transducers measure changes in the shaft stretching to calculate the torque. This measurement is conducted using strain gauges bonded to the shaft, which measure the strain induced in the shaft by the applied torque or force.

The direct torque measurement approach requires the following tools:

- A direct torque measuring device with a contact-free sender and receiver integrated into the impeller shaft;
- A pre-calibrated measuring device;
- A display of measured values on an HMI;
- Granulation endpoint determination function; and
- Set points for granulation endpoint determination on an HMI.

Figure 2 shows a comparison between the impeller current and the impeller direct torque using a wireless telemetry system for an ACG 1200 L HSM mixer. The left vertical axis denotes the current in amperes, and the right vertical axis denotes the impeller direct torque in newton meters. The red line indicates the pattern of the impeller current, and the blue line indicates the pattern of the impeller direct torque. The graph clearly shows that fluctuations in the impeller current are more frequent than fluctuations in the impeller torque even though the values of torque range from 0 to 4,000, while the values of impeller current range from 0 to 90. This precision in
Figure 2
Comparison of calculated impeller current versus impeller direct torque (ACG 1200 L HSM)

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