eye on excipients

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Manufacturers favor continuous direct compression of tablet formulations because it is economical and efficient, but the process presents a variety of manufacturing challenges related to content uniformity, compactibility, and flow. This edition of "Eye on Excipients" explores a method for incorporating a co-processed excipient into a tablet formulation to facilitate direct compression tableting and create more robust tablets.

Although traditional batch processing has long been the norm in the pharmaceutical industry, drug product manufacturers have begun to shift toward continuous manufacturing as a more sustainable, economical, and time-efficient method. Key benefits of continuous manufacturing include better process control, simpler scale-up or none at all, enhanced safety margins, increased productivity, and improved quality and yields. In addition, the equipment needed for continuous manufacturing is much smaller than its batch counterpart, and it operates at a steady state, which facilitates automation and process monitoring.

Tablets are the most common dosage form, comprising around 70 percent of the global oral drug delivery market [1]. As a result, many formulators transitioning to continuous operations have led with direct compression (DC) tableting. Continuous DC tableting allows for the ingredients to be processed and compressed seamlessly without a granulation step, making it more economical than traditional batch tableting.

While direct compression of a formulation improves efficiency, the lack of an intermediate granulation step can present a challenge because most pharmaceutical ingredients do not have inherent binding properties. High-dose tablets may lack sufficient tensile strength if the active pharmaceutical ingredient (API) is not easily compressible, while low-dose formulations may be difficult to blend uniformly. Additionally, since some APIs are hygroscopic and thermolabile (heat sensitive) in nature, they can be difficult to compress. Excipients, such as diluents, fillers, and binders can play a significant role in improving a formulation's content uniformity, flow, and compaction properties as well as the resulting tablet's tensile strength.

Incorporating co-processed excipients

One of the keys to overcoming these challenges is to select excipients that both integrate well with the formulation and offer suitable powder flow properties, to ensure consistent tablet weight and content uniformity. Choosing the correct excipient can also help manufacturers avoid ingredient segregation during the blending process, improve flow and transfer to the equipment train, and achieve proper lubrication for one-step mixing.

Co-processed excipients, which are a combination of two to three excipients developed via co-processing, may be the answer. They offer functionalities exceeding those of traditional physical excipient blends, allowing formulators to reduce manufacturing steps while ensuring tablet quality. Co-processed excipients lend themselves well to continuous operations because they are engineered to achieve the synergistic properties of a tableting blend's key components in a single, highly flowable and compressible granular material [2].

Formulators whose DC tableting operations are faced with particle segregation, poor API content uniformity, and excipients plugging or blocking the manufacturing process should seek out an excipient that improves powder flow and tablet compactibility, thus helping to maintain API uniformity within the tablets.

This article describes a study in which researchers, using different grades of a co-processed excipient, examined powder flow, compactibility, and tablet tensile strength, during the direct compression process. For the study, the researchers selected a silicified microcrystalline cellulose (Avicel SMCC, DuPont) that consists of 98 percent w/w microcrystalline cellulose (MCC) and 2 percent w/w silicon dioxide. They chose SMCC because it does not alter the chemical structure of MCC yet exhibits improved compaction and powder flow properties.

The researchers first examined the flow characterization of the SMCC according to the pharmacopoeial methods [3], and performed a variety of simple and rapid tests, such as

Figure 1

Angle of repose for different SMCC grades versus MCC

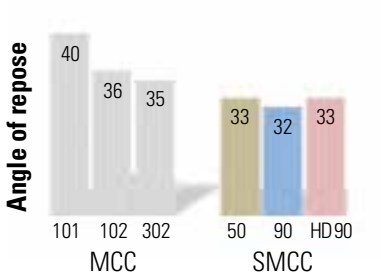


Figure 2

Carr's compressibility index for different SMCC grades versus MCC

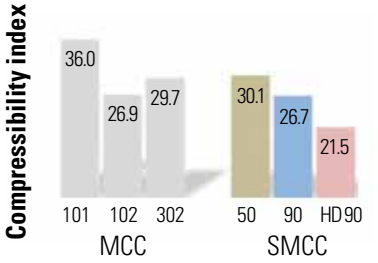
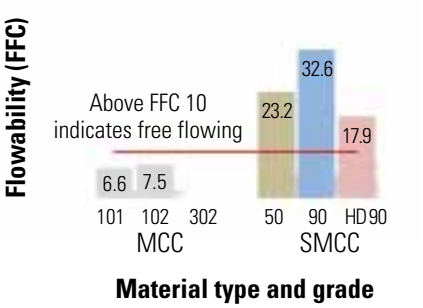


Figure 3

FT4 powder rheometer flow-test data for different SMCC grades versus MCC



angle of repose, Carr's compressibility index, and powder density (bulk and tapped). In addition, they conducted advanced flow tests using a powder rheometer (FT4, Freeman) and ring shear tests, as well as scanning electron microscopy (SEM) to characterize the excipient's powder morphology. The researchers then used a compaction simulator—an instrumented single-punch hydraulic tablet press that simulates the operation of a rotary tablet press—to explore whether the co-processed excipient can help to formulate more-robust tablets in direct compression than the traditional excipient (Avicel MCC, DuPont).

Powder flow tests

The researchers used a powder flow tester for the angle of repose test, a characteristic test to determine interparticle friction based on the three-dimensional angle made by a cone-like pile of material. For the procedure, researchers used a 100-millimeter-diameter base plate and fixed a funnel 40 millimeters above the plate, allowing the powder to fall on the base plate through a 10-millimeter funnel orifice, without any vibration to the funnel or base. The quantity of powder was sufficient to form a cone, with the excess falling over the edge of the base plate.

The height of the cone was measured with a calibrated digital Vernier, and the angle of repose was calculated with the following formula:

$$\tan(a) = \frac{height}{(0.5\ base)}$$

The researchers measured the angle of repose in degrees, with an angle greater than 66 degrees indicating "very, very poor" flowability and 25-30 degrees indicating "excellent" flowability. As Figure 1 indicates, the SMCC grades demonstrated increased flowability compared to the MCC grades.

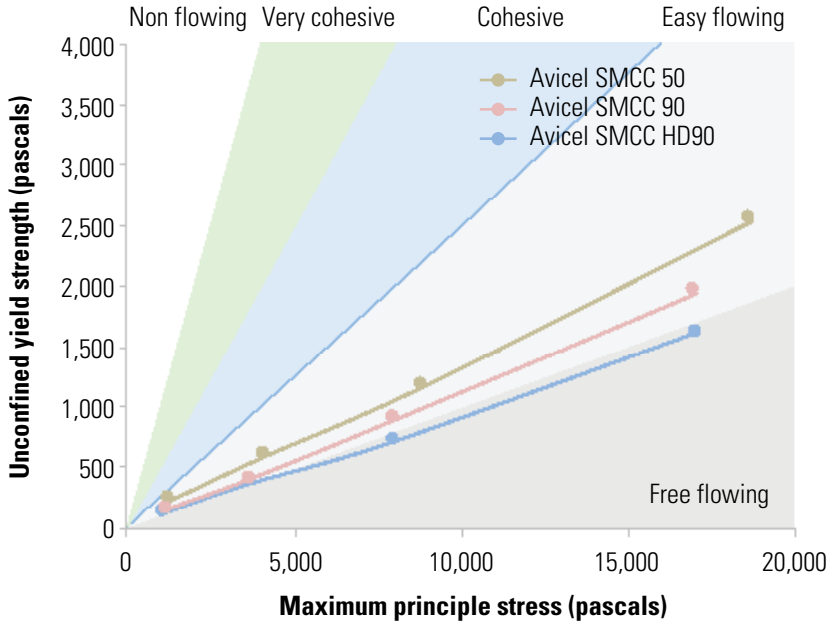
The researchers then measured the materials' bulk and tapped densities using a bulk and tap density apparatus (Electrolab, India) and compared the values. Tapped density is a material's bulk density after mechanical tapping of a sample in a graduated measuring cylinder. In a free-flowing powder, there is less interparticle friction, so the bulk and tapped density values will be closer to each other than in a poorly flowing powder.

Using the bulk and tapped density values, the researchers determined the Carr's compressibility index and Hausner ratio for each material. A compressibility index value greater than 38 percent is considered "poor," while 16 to 20 percent is considered "excellent." As Figure 2 indicates, the SMCC grades demonstrated increased flowability compared to the MCC grades.

The flow-test data (Figure 3) and ring-shear-test data (Figure 4) also indicate that SMCC is a free-flowing material that allows for tablets with excellent weight and content unifor-

Figure 4

Ring-shear-test data for different SMCC grades



mity, attributes that can be difficult to achieve in DC processes.

Tablet compaction tests

The tablet compaction cycle has three different stages that determine the tablets' mechanical and physicochemical characteristics: pre-compression, main compression, and ejection. Using the compaction simulator (ESH, UK) the researchers focused on measuring all the parameters of the compaction cycle. They then evaluated the material characteristics by correlating and computing parameters, along with finished tablet properties such as weight variation, hardness, thickness, and diameter.

For the compaction trials, the researchers fitted the compaction simulator with 13-millimeter-diameter, flat-face punches and compacted about 500 milligrams of powder into tablets. The contact time, a general indicator of compaction speed, was 0.028 seconds. To vary the maximum compression pressures, the researchers kept the upper punch displacement profiles as sine waves with different amplitudes. They followed pre-lubrication with magnesium stearate, to avoid frictional damage of the punch and die set.

Researchers then packed the prepared tablets into HDPE bottles, with a separate bottle for each different compression force, and stored the bottles in a desiccator with controlled humidity for complete physical relaxation. After 24 hours of storage, they analyzed the tablets for weight variation, hardness, thickness, and diameter and then calculated the compaction slope value and tablet tensile strength based on the hardness and compaction force data.

During the compaction process, the tablet tensile strength increases proportionally with the compaction pressure. The specific increase of the tensile strength (as indicated by the slope of the curve in Figure 5) is higher for the SMCC grades than for the MCC.

As Figures 1 through 5 show, the co-processed SMCC excipient exhibits excellent flow and compaction properties, making it more suitable for DC tableting and continuous manufacturing processes than traditional MCC.

In addition, the surface morphological studies of the SMCC (Figure 6) show uniform distribution of colloidal silicon dioxide particles over the surface of the MCC particles, which is essential for the excipient's improved functional characteristics. To some extent, deposition was also observed in the inter-spatial structure of the MCC particles. The overall surface examination and the flow studies of SMCC provides important morphological information about the improvement in the functional characteristics and particle surface modifications.

Conclusion

The study shows that SMCC's properties extend beyond the traditional MCC excipient capabilities, with improved binding and advanced physical and morphological properties. In addition, this demonstrates

Figure 5

Placebo tablet tensile strength at different compression pressures (higher slope indicates better compactibility)

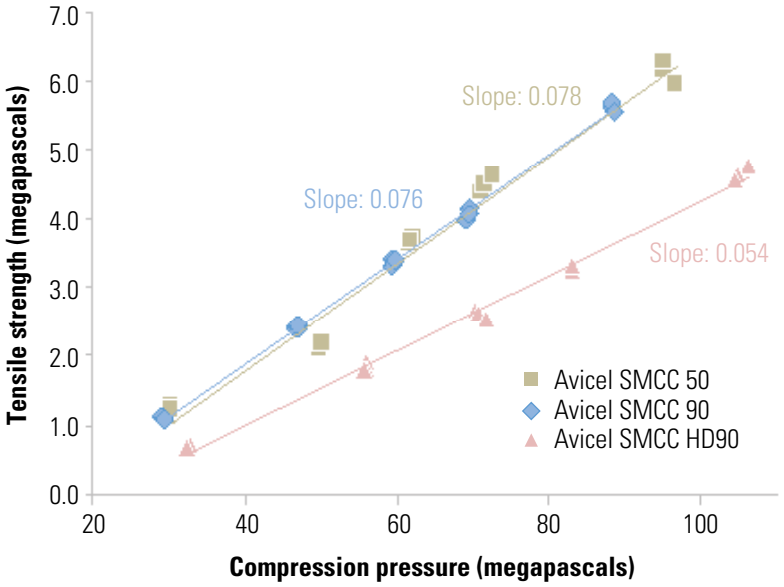
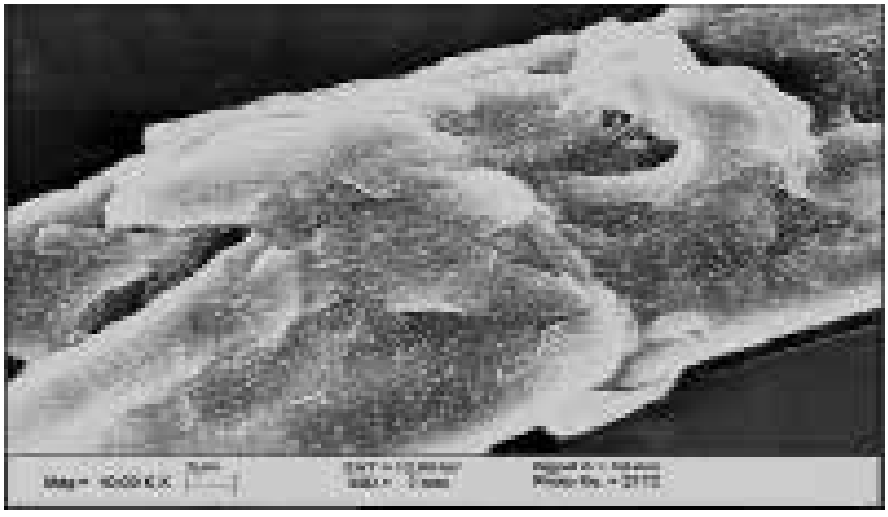


Figure 6

SEM image of SMCC (white spots indicate homogeneous distribution of silicon dioxide over the MCC particle)



that a co-processed excipient such as SMCC lends itself to improved flow and better compactibility during compression, which results in lower tablet weight variation and better content uniformity. These traits allow formulators to produce a robust tablet as well as facilitate DC or alternative continuous manufacturing processes.

As the trend toward continuous pharma manufacturing continues, it is essential that manufacturers are equipped with excipients that are optimized for such operations, since incorporating the incorrect excipient can cause a manufacturing process to malfunction. This study shows that co-processed excipients, such as SMCC, can help solve many continuous manufacturing challenges by improving flow, compactibility, and tablet tensile strength. Formulators should consider that these attributes may make co-processed excipients such as SMCC beneficial in processes besides DC tableting as well, such as multi-particulate systems or dry granulation. *T&C*

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