This article describes a study that assessed the performance of a lactose-HPMC co-processed excipient in the manufacture of modified-release tablets using a direct-compression blend and an instrumented tablet press. Ibuprofen was used as the model API.

Pharmaceutical developers have long recognized that direct compression (DC) is the simplest and thus preferred method of manufacturing tablets. Figure 1 compares the number of processing steps required of three different methods of preparing powders for tabletting: wet granulation (batch process), dry granulation (semi-continuous), and DC (continuous process).

The wet granulation technique entails the most steps, but few of them are potential sources of variability. Using dry granulation to improve a formulation’s processability is simpler—it uses a roller compactor instead of a wet granulator—but compressing the raw materials before they reach the press usually reduces the formulation’s compressibility. DC, however, is regarded as an ideal continuous process that has fewer steps that are prone to variability.

Despite the low number of processing steps DC formulations require, they are still a challenge. To make robust tablets, the formulations must include excipients with excellent functional properties, such as good flowability, dilution potential, compressibility, and compactibility. In
fact, these must be intrinsic excipient qualities. Table 1 lists examples of how several material attributes relate to functional properties.

Excipients that perform inadequately can cause segregation that leads to poor content uniformity, inconsistent tablet weights, inferior tablet strength and, ultimately, dissolution failure. Preventing these deficiencies requires excipient combinations that balance flowability and compressibility, and several manufacturers offer co-processed excipients to do just that. Table 2 lists some of them.

**Benefits of DC-grade HPMC**

The recent introduction of a DC-grade hydroxypropyl methylcellulose (HPMC) 2208 is a significant step in facilitating the task of formulators, especially to create modified-release (MR) forms. That's because HPMC-based hydrophilic matrix tablets constitute a significant percentage of all MR solid oral dosage forms [1]. The benefits of HPMC-based MR tablets include versatility in accommodating active pharmaceutical ingredients (APIs) that have a wide range of physicochemical properties. Such tablets are also simple to design, easy to manufacture, and inexpensive.

**Table 1**

<table>
<thead>
<tr>
<th>Material attributes</th>
<th>Flowability</th>
<th>Blending</th>
<th>Mechanical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial size distribution</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Particle shape</td>
<td>X</td>
<td>-</td>
<td>-</td>
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<tr>
<td>True density</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Bulk density</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Particle surface area</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Particle surface energy</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Cohesiveness</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Britteness/elastic modulus</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

In conventional form, HPMC is a fine powder with a fibrous morphology that benefits a tablet’s mechanical properties. Its fibrous nature, however, limits flowability and can make it difficult to use in DC processes. However, the new DC-grade HPMCs—Benecel PH DC from Ashland and Methocel DC2 from Dow—have particles whose morphology improves flowability. These superior attributes help formulators delineate the critical process parameters (CPPs) and streamline the complex interplay between product and process. This has become even more important since the FDA introduced its Quality by Design (QbD) and other initiatives, which have prompted phar-
maceutical manufacturers to focus on developmental practices that help ensure—from the start—that product quality aligns with patient safety, product efficacy, and product reliability.

**Co-processed HPMC and lactose**

Retalac (Meggle USA, Pawling, NY) is a DC-grade, co-processed excipient that contains equal parts HPMC and lactose and that is intended for use in MR tablets. Co-processed, the two excipients perform better than a simple blend of them. Indeed, co-processing improves the functional properties (e.g., flow and compressibility) of the excipients while maintaining their independent chemical characteristics [2]. The first objective of the study described here was to assess the compressibility and tabletability of a model formulation containing Retalac. The second objective was to outline the advantages of an instrumented tablet press during early formulation development stages to screen and develop MR tablets made using a DC-grade excipient.

**Experiment**

**Materials.** Retalac was obtained from Mutchler, Harrington Park, NJ; ibuprofen from BASF, Florham Park, NJ; and magnesium stearate from Sigma-Aldrich, St. Louis, MO.

**Methods.** A study of the compaction profile, the lubricant sensitivity, and the strain-rate behavior of a DC formulation (ibuprofen 30 percent, Retalac 69.5 percent, magnesium stearate 0.5 percent) was performed using an instrumented benchtop, 10-station rotary tablet press (Piccola, SMI, Lebanon, NJ) equipped with 7/16-inch round, standard concave B tooling. Data acquisition, analysis, and data representation were performed using The Director software from SMI.

One-kilogram powder blends were prepared as follows: Retalac and ibuprofen were passed through a 20-mesh sieve and magnesium stearate through an 80-mesh sieve. Powders were then combined in a V-type blender (Globepharma, New Brunswick, NJ) for 10 minutes at 20 rpm.

**Compaction profile.** The goal of this study was to assess the effect of compression force on the powder blend’s tabletability. It was performed on tablets weighing 400, 500, and 600 milligrams (mg) at compression forces ranging from 50 to 300 megapascals (MPa) at a constant turret speed of 25 rpm. The effect of pre-compression on the compaction profile was evaluated for 400- and 600-mg tablets.

**Lubricant sensitivity.** This study was performed on 500-mg placebo tablets to see how different levels of lubricant (0.25 and 0.5 percent) affected tablet tensile strength at various compression forces.

**Strain rate.** This study evaluated the effect of turret speed on variation of tablet properties. It was performed on 500-mg tablets at five different turret speeds.

The flow property of the excipient, API, and powder blend was evaluated using a powder flow analyzer (Texture Technologies, Hamilton, MA). Physical and mechanical properties (weight, thickness, and breaking force) of the tablets were analyzed using a SmartTest 50 (Sotax, Westborough, MA). Tablet friability was analyzed using an FT 2 friability tester (Sotax).

Tablet breaking force was normalized to account for tablet geometry (size and shape) to yield tensile strength (σ) and is given by the following equation for round, convex tablets (from USP <1217>):

\[
\sigma_x = \left( \frac{10F}{\pi D^2/Dw} \right) \left( \frac{2.84H}{W} + \frac{0.126H}{W} + \frac{3.15W}{Dw} \right) + 0.01
\]

where

- \( F \) = Breaking force
- \( D \) = Tablet diameter
- \( H \) = Tablet thickness
- \( W \) = Central cylinder thickness (tablet wall height)

**Tablet press instrumentation and parameterization**

Understanding powder behavior under dynamic conditions is crucial in the early development stage in order to develop robust formulations, and data obtained during development can be vital in transferring the formulation to a production-scale press. Instrumentation is also essential to a QbD approach to process development and lifecycle management. It helps researchers to identify CPPs, define the design space, and understand both the product and the process under development. These parameters are also useful metrics in monitoring the quality of the process after the product gains regulatory approval.

**Results**

**Compaction profile.** Physical testing of the tablet was performed at two stages: approximately 10 minutes after compression and 24 hours after compression. Samples were kept in a sealed container during the 24-hour holding period. The extended hold time had no noticeable effect on the thickness or friability of the samples, but it did affect the tensile strength of all the formulations studied. In tablets that included the API, tensile strength increased by 6 to 10 percent after 24 hours. This effect can occur in lactose-based formulations due to the amorphous particles that can absorb moisture from the air, which allows the formation of crystalline bonds that were not present immediately after compression [3].

When the tabletting process included pre-compression, the increase in tensile strength was 9 to 10 percent, without it, the increase was 6 to 7 percent. This relative increase in strength derives from an increase in interparticle solid bonds. Ibuprofen and HPMC are both prone to air entrapment, which increases porosity and thereby reduces interparticle contact. The relative increase in strength—coupled with thickness measurements that showed that the pre-compressed tablets were slightly thinner than those made without pre-compression—indicate that this formulation’s tablets include entrapped air that was countered by the pre-compression force.
Tables made from the blends that included the API exhibited significantly less tensile strength than those made from a similarly lubricated placebo blend. As shown in Figure 2, the placebo with 0.5 percent magnesium stearate achieved a tensile strength of 3,230 kilopascals (kPa) at 300 MPa main compaction pressure; the API blend with 0.5 percent magnesium stearate achieved a tensile strength of only 1,780 kPa at 325 MPa main compaction pressure, a decrease in tablet strength of more than a 45 percent. The relative difference between the formulations' strengths decreases to approximately 25 percent at around 100 MPa. It can also been seen that the active blend is near its maximum tensile strength at 325 MPa because the curve becomes increasingly horizontal.

**Lubrication sensitivity.** The amount of magnesium stearate in the formulation had a small but noticeable impact on tablet strength. Decreasing the lubricant in the placebo blend to 0.25 percent resulted in an approximately 6 percent increase in tensile strength. As shown in Figure 3, ejection forces for both blends drop off sharply, with the 0.5 percent blend dropping off sooner. This is the telltale sign of over-lubrication, which occurs when excess lubricant is forced from the compact and coats the die walls. In this case, reducing the amount of lubricant would increase tensile strength and decrease dissolution times without causing ejection forces or tooling wear to increase significantly. Figure 3 also shows a slight decrease in ejection forces at the highest compaction pressures for blends containing API, suggesting that they might benefit from a slight reduction in lubricant level to 0.40 or 0.45 percent.

All formulations in the compaction-profile and lubrication-sensitivity studies exhibited very low ejection forces. The API-containing blends showed higher ejection forces than the placebo, but ejection forces remained less than 200 newtons for all tablet weights and compaction levels. This is impressive given that the formulation contains 30 percent ibuprofen and almost 35 percent lactose, both of which are known to induce high ejection forces. The co-processing of HPMC with lactose monohydrate has clearly mitigated one of the negative characteristics of lactose (high ejection forces) while preserving its effectiveness as a binder.

**Strain rate.** Brittle materials fracture very quickly when they deform, but materials that deform plastically need more time to assume the shape they're forced into. As a result, brittle materials are relatively unaffected by the rate at which compaction occurs, and plastic materials form weaker compacts at higher production speeds. Lactose and ibuprofen exhibit brittle properties, while HPMC deforms plastically. This raises the question of which behavior will dominate in a blend of these materials.

Strain-rate studies can answer this question by comparing the strength of tablets produced at varying press speeds. Figure 4 shows that the blend used in this study is strain-rate sensitive and the decrease in the tensile strength of the tablets is characteristic of plastically deforming materials. The figure also shows that the trend levels off after the tangential velocity reaches 400 millimeters per second. In some blends, tensile strength remains steady, while in oth-

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**Figure 2**

Compaction curves of placebo and active tablets (total weight 500 milligrams)

![Compaction curves of placebo and active tablets](image)
**Figure 3**

Ejection force versus compaction pressure for placebo and active tablets

**Figure 4**

Tensile strength-compaction pressure ratio versus tangential velocity of tablet press turret
ers it decreases again shortly after leveling off. Further study at higher tangential velocities would be required to determine the category to which this formulation belongs.

Conclusions

The first goal for this study was to investigate the tabletability of a model DC formulation based on Retalac. In the compaction profile, viable tablets were made at 100 to 300 MPa, and it was observed that Retalac retained lactose's ability to increase tablet tensile strength as long as 4 hours after compression. The lubrication study showed that Retalac can maintain relatively low ejection forces, even at high compaction levels. The strain-rate study revealed that the formulation is sensitive to loading rate, which may or may not lead to issues when scaling up to production; this would require monitoring during the development process.

But even if a small reduction in tablet press speed were required due to strain rate sensitivity, it would likely be outweighed by the time and cost savings of eliminating the equipment train, labor, and validation requirements of granulating, wet-sizing, drying, milling, and final blending. These findings demonstrate that Retalac is a viable option for DC formulations that use HPMC.

The second goal of this study was to demonstrate the advantages of an instrumented tablet press in formulation development, and the studies discussed above are based on data acquired by the tablet press's instrumentation. These data are very helpful. Ejection forces, for example, must be quantified to identify over lubrication. The force during the main compression event must be known to plot a compaction curve, which formulators use to determine the maximum tensile strength of a formulation. Likewise, performing an effective strain-rate study requires knowing the speed of the turret and verifying that a constant compressive force is maintained.

In this era of QbD and total process understanding, process instrumentation isn't just a powerful development tool, it's the key to unlocking the potential of your research and development operations.

References


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