This article describes a novel MCC and presents a study in which it is shown to decrease segregation in a low-dose tablet compared to a tablet made using an industry-standard MCC.

Content uniformity of the active pharmaceutical ingredient (API) in tablets is critical because it ensures patients receive the same dose from tablet to tablet. But it becomes increasingly difficult to attain content uniformity as the API dose decreases because the API segregates more readily from the formulation’s excipients.

Wet and dry granulation limit segregation, but both techniques add time and cost to tablet manufacturing. Manufacturers would prefer to simply blend the ingredients and send them to the tablet press. Such formulations are known as direct-to-press blends, and the process is called direct compression. This article describes a novel microcrystalline cellulose (MCC) that limits segregation of APIs in low-dose tablets, allowing formulators to more easily create direct-to-press blends [1]. It also presents the results of a study that show that the novel MCC provided better content uniformity than an industry-standard MCC in tablets containing a low-dose API.

Compactability and flowability

Manufacturing a tablet by direct compression requires taking many factors into consideration, including the particle size, shape, flow, and compressibility of the materials and how those properties affect content uniformity. The process itself must also be evaluated because segregation can often occur during blending and/or in the hopper and feed system of the tablet press.

Figure 1 illustrates the tradeoff between compactability and flowability in all MCCs. The novel MCC discussed here maintains a standard degree of compactability while improving flowability (repose angle of 34 degrees), which minimizes segregation during blending and enables manufacturers to gravity-feed blends during direct compression.

Particle properties

The compactability index was calculated using tablet hardness data from each MCC grade based on a common tablet formulation. The hardness of tablets containing PH-101 was set at 100. Each tablet comprised 70 percent acetaminophen and 30 percent MCC and was compressed to a target tablet weight of 500 milligrams on a static tablet press at 7 kilonewtons in a 11.3-millimeter-diameter die by a flat-faced punch. The flowability of each MCC was quantified based on its repose angle. See Figure 1.

Table 1 lists some common tablet properties. The bulk density of the novel MCC is nearly equivalent to that of the PH-101 and shows the best repose angle of the MCCs tested. The micrograph in Figure 2 shows that the novel MCC comprises predominately round, aggregated particles. This particle shape greatly contributes to the novel MCC’s superior flow. A cross-sectional view of the particle reveals its porosity (Figure 3). This porous structure improves the MCC’s plastic deformation, which allows it to provide good compactability during direct compression.
As for segregation, it typically is influenced by whether the blend is ordered (interactive) or random. Segregation is rare in ordered blends because there is a high amount of interaction between the API and excipient particles. The opposite is true of random blends, where the low level of interaction between the API and excipient particles frequently leads to greater segregation (Figure 4).

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Bulk density (g/cm³)</th>
<th>Average particle size (microns)</th>
<th>Repose angle (degrees)</th>
<th>Oil-absorbing capacity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KG-1000</td>
<td>0.12</td>
<td>50</td>
<td>57</td>
<td>270</td>
</tr>
<tr>
<td>KG-802</td>
<td>0.21</td>
<td>50</td>
<td>49</td>
<td>200</td>
</tr>
<tr>
<td>PH-101</td>
<td>0.29</td>
<td>50</td>
<td>45</td>
<td>190</td>
</tr>
<tr>
<td>PH-102</td>
<td>0.30</td>
<td>90</td>
<td>42</td>
<td>180</td>
</tr>
<tr>
<td>PH-200</td>
<td>0.35</td>
<td>180</td>
<td>36</td>
<td>150</td>
</tr>
<tr>
<td>PH-301</td>
<td>0.41</td>
<td>50</td>
<td>41</td>
<td>120</td>
</tr>
<tr>
<td>PH-302</td>
<td>0.42</td>
<td>90</td>
<td>38</td>
<td>200</td>
</tr>
<tr>
<td>Novel MCC [1]</td>
<td>0.29</td>
<td>100</td>
<td>34</td>
<td>190</td>
</tr>
</tbody>
</table>

Levothyroxine is an API known to segregate in low-dose formulations. It was chosen as a model API for several experiments in which two different grades of MCCs were tested to determine which material would limit segregation better in low-dose formulations of levothyroxine. Highly water soluble APIs typically show a low triboelectric charge because of their hydrophilicity. These low-charge materials are likely to have less interaction with the excipients and thus are more likely to result in a random blend that has a high potential to segregate. Figure 5 shows the results of tests conducted on multiple APIs to assess their triboelectric charge. The tests of levothyroxine gave a result of 1.1 nanocoulombs per gram (nC/g).

The model formulation used in this experiment contained levothyroxine (0.1 percent), MCC (80 percent), crosscarmellose sodium (2 percent), D-mannitol (16.9 percent), and magnesium stearate (1 percent). To assess the anti-segregation effect, the novel MCC was compared with the industry standard MCC, PH-102.

The process mixed the levothyroxine, MCC, crosscarmellose, and mannitol in a V-type blender for 117 minutes. Then the magnesium stearate was added and the powders were blended for an additional 3 minutes. During blending, the samples were taken every 30 minutes to determine the effect of the process on blend uniformity. At the end of the process, the blend was discharged and compressed into tablets on a rotary press.
During that process, tablet samples were taken every 5 minutes and tested for content uniformity.

To analyze the results and see whether the different MCCs showed any difference in segregation of the levothyroxine, it was first necessary to determine whether to base the results on weight variance or on content uniformity. For this we relied on USP General Chapter <905>, which states that tablets containing less than 25 percent API should use an acceptance value based on content uniformity. The acceptance value was calculated as shown in Equation 1:

\[ |M-X| + ks \]

where
- \( M \) is the reference value
- \( X \) is the mean of individual contents
- \( k \) is the acceptability constant, and
- \( s \) is the sample standard deviation.

In this case, the maximum allowable acceptance value was 15 percent. Figure 6 presents the results.

After the 120-minute blending process, the acceptance values were 12.7 percent for the PH-102 and 7.3 percent for the novel MCC, both within the 15 percent threshold. Results from multiple tests of the tablet samples containing PH-102 MCC—taken at 5-minute intervals—showed the acceptance values were 18.9 percent, 13.8 percent, and 16.9 percent. This shows that the PH-102 did not adequately limit levothyroxine segregation after the blend was transferred to the hopper and passed through the tablet press. In contrast, tests on tablet samples that included the novel MCC and taken at the same intervals showed acceptance values of 13.0 percent, 14.1 percent, and 14.0 percent. These results indicate that using the novel MCC can limit the potential segregation in formulations containing a low dose of levothyroxine.

**Figure 6**

Acceptance values of powder blends and tablets containing different MCCs

In this case, the maximum allowable acceptance value was 15 percent. Figure 6 presents the results.

After the 120-minute blending process, the acceptance values were 12.7 percent for the PH-102 and 7.3 percent for the novel MCC, both within the 15 percent threshold. Results from multiple tests of the tablet samples containing PH-102 MCC—taken at 5-minute intervals—showed the acceptance values were 18.9 percent, 13.8 percent, and 16.9 percent. This shows that the PH-102 did not adequately limit levothyroxine segregation after the blend was transferred to the hopper and passed through the tablet press. In contrast, tests on tablet samples that included the novel MCC and taken at the same intervals showed acceptance values of 13.0 percent, 14.1 percent, and 14.0 percent. These results indicate that using the novel MCC can limit the potential segregation in formulations containing a low dose of levothyroxine.

**Reference**

1. Ceolus UF-702 from Asahi Kasei, Tokyo, Japan.

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**Further reading**

Find more information about how to prevent or mitigate segregation of direct-to-press blends in the article "Identifying and controlling segregation in tablet press feed systems," by Kerry Johanson. It appeared in the May 2017 issue.

Another Johanson article, "Relating flow properties to process behavior in tablet presses and capsule filling machines," appeared in the May 2014 issue.