In this edition of the column, researchers from Nisso present the results of a study that examined how the molecular weight (MW) of different hydroxypropyl cellulose (HPC) grades affected the characteristics of granules and tablets prepared by two wet granulation methods: high-shear and fluid bed.

Wet granulation is one of the most commonly used methods of developing solid dosage drug products. Among the advantages of this classical granulation method over other technologies are a narrow particle size distribution (PSD) of the granules, few fine particles that yield little dust, more consistent powder flow, better control of granule size, very good binder homogeneity, and good powder compactability.

The most important excipient group in a successful wet granulation formulation is the binder. Within this group are polymers with different chemistries, mechanical properties, and viscosity ranges. The polymer binder HPC has attracted the attention of formulators in the last decade due to its superior mechanical properties, chemical stability, and multi-functionality. This cellulosic ether appears to work even in challenging formulations with high-dose, poorly compressible drug products, where other binders usually fail. Low-viscosity (low-MW) HPC grades are used as a binder for all types of wet granulation including high-shear, fluid-bed, extrusion, and melt granulation. To select the suitable grade, scientists often must conduct many experiments, adjusting the desired powder and tablet characteristics. In this study, we focused on the influence of the HPC MW on the granule and tablet characteristics in fluid-bed and high-shear wet granulation.

### Materials and methods

The study used HPCs with MWs of 40,000 daltons (Nisso HPC-SSL and SSL SFP from Nippon Soda, Tokyo, Japan), 100,000 daltons (Nisso HPC-SL and SL FP), and 140,000 daltons (Nisso HPC-L and L FP). Paracetamol (Atabay, Istanbul, Turkey) was used as a model active pharmaceutical ingredient (API); use level was 85 percent by weight. Croscarmellose sodium (Vivasol, JRS Pharma, Patterson, NY) was used as a superdisintegrant and magnesium stearate (Lehmann & Voss, Hamburg, Germany) was used as a lubricant. A fluid-bed granulator (Solidlab 2, Bosch, Waiblingen, Germany) and high-shear granulator (Mycromix, Bosch) were used for the granulation of pure paracetamol. The PSD of the granules was analyzed by laser diffraction.

### Table 1

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (mg)</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>510.00</td>
<td>85.00</td>
</tr>
<tr>
<td>Binder</td>
<td>60.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>24.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>6.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>600.00</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>HPC grade</th>
<th>Molecular weight</th>
<th>Median particle size (µm)</th>
<th>Average viscosity (mPa•s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSL</td>
<td>40,000</td>
<td>85</td>
<td>2.5</td>
</tr>
<tr>
<td>SSL SFP</td>
<td>40,000</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>SL</td>
<td>100,000</td>
<td>160</td>
<td>5.0</td>
</tr>
<tr>
<td>SL FP</td>
<td>100,000</td>
<td>95</td>
<td>5.0</td>
</tr>
<tr>
<td>L</td>
<td>140,000</td>
<td>160</td>
<td>8.0</td>
</tr>
</tbody>
</table>

1. By laser diffraction
2. At 20°C; 2% aqueous solution

### Table 3

<table>
<thead>
<tr>
<th>HPC grade</th>
<th>Inlet temperature</th>
<th>Inlet conditioning</th>
<th>Air flow</th>
<th>Spray rate</th>
<th>Spray pressure</th>
<th>Micro-climate pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSL</td>
<td>80°C</td>
<td>Dehumidifying (1.8 g/kg)</td>
<td>130-170 m³/h</td>
<td>70 g/min</td>
<td>0.6 bar</td>
<td>0.1 bar</td>
</tr>
<tr>
<td>SL</td>
<td>80°C</td>
<td>Dehumidifying (1.8 g/kg)</td>
<td>130-170 m³/h</td>
<td>70 g/min</td>
<td>0.6 bar</td>
<td>0.1 bar</td>
</tr>
<tr>
<td>L</td>
<td>80°C</td>
<td>Dehumidifying (1.8 g/kg)</td>
<td>130-170 m³/h</td>
<td>70 g/min</td>
<td>0.6 bar</td>
<td>0.1 bar</td>
</tr>
</tbody>
</table>
HPC-SL FP, and HPC-L FP were used in the high-shear granulation. They were added dry, with purified water serving as the granulation liquid.

**Results and discussion:**

**Fluid-bed granulation**

Each HPC aqueous solution was prepared to the same 8 percent concentration. The average viscosity of the different solutions, expressed in millipascal-seconds, was 20 mPa·s for the SSL, 65 mPa·s for the SL, and 200 mPa·s for the L. Table 3 lists the main process parameters for fluid-bed granulation.

**PSD of the granules.** A strong effect of the HPC’s MW on the granules’ PSD was observed. The lowest MW grade (HPC-SSL) produced finer granules with a very narrow PSD (Figure 2). The coarsest granules, with a broader PSD, were observed to result from HPC-L, which had the highest MW of the tested grades. There was a clear relationship between the HPC’s MW and the size of the granules: SSL < SL < L. This shows that changing the HPC grade makes it possible to modulate the granule particle size and PSD without changing the product’s formulation or granulation parameters.

**Powder compactability.** The granules obtained were formed into tablets at five different compression forces (Figure 3). The moisture content of all the powder blends was similar, thus its effect on the powder compaction properties can be excluded. At compression forces up to 15 kilonewtons (kN), the powders showed approximately the same compactability. At higher compression forces, the granules made with HPC-SSL demonstrated much better compaction properties and yielded the highest tablet breaking forces. A possible reason for the superior deformability of the SSL could relate to the mobility of the polymer chain in the dry powder. HPC grades SL and L have higher MW’s (100,000 and 140,000) and are more sterically bound in dry form, creating a binder with more elasticity and less deformability.
Tablet disintegration. The disintegration of the tablets also showed a dependence on the HPC MW. It is well known that a high viscosity inside the tablet matrix can prolong disintegration by reducing water uptake. Figure 4 shows the disintegration time of tablets with a breaking force of 200 newtons.

As expected, tablets made using the lowest-viscosity (lowest-MW) HPC (SSL) disintegrated fastest, followed by SL and L.

Tablet friability. All the tablets showed acceptable friability results (Figure 5). No impact of the HPC MW was observed.

Binder solution concentration. Though this study did not examine the effects of binder concentration, it is expected that the low MW of HPC-SSL would allow a higher concentration of polymer in the binder solution while maintaining an acceptable viscosity. In industry practice, it is typical for binder solutions to be prepared to a viscosity of approximately 200 to 500 mPa·s. If the binder solution's viscosity were fixed at 200 mPa·s, the corresponding polymer concentrations would be roughly 20 percent for SSL, 11 percent for SL, 8 percent for L. The higher solids content of an SSL binder solution would allow faster batch times and require less drying energy. For example, if a batch required a spraying time of 120 minutes with an 8 percent solution of HPC-L, the same batch could be completed in 48 minutes using a 20 percent solution of HPC-SSL. Correspondingly, the energy required would decrease by more than half, batch time would shorten, and water usage would decrease.

Conclusions: Fluid-bed granulation. In this study:

The largest granules were produced when the highest-MW binder (HPC-L) was used. Granule size increased as the HPC's MW increased: SSL < SL < L.

The narrowest PSD of the obtained granules was achieved using the lowest-MW binder (HPC-SSL).

The compaction properties of granules that included the lowest-MW binder (HPC-SSL) were best when compressed at high compression forces (>15 kN).
The tablets that disintegrated fastest used the lowest-MW binder (HPC-SSL) due to its very low viscosity.

Results and discussion:
High-shear granulation

For the high-shear granulation, fine powder grades of HPC were used as binder. They included HPC-SSL SFP with a median particle size ($D_{50}$) of 20 microns (µm), HPC-SL FP ($D_{50}$ of 95 µm), and HPC-L FP ($D_{50}$ of 95 µm). Tables 4 and 5 show the granulation parameters and drying conditions used.

PSD of the granules. Recall that in fluid-bed granulation, the MW of the dissolved binder had a significant impact on granule size. However, in high-shear granulation using a dry binder addition, the MW had only a minor effect on the granules' PSDs (Figure 6). The lowest-MW grade (HPC-SSL SFP) produced slightly fewer fines, but the differences between all the grades were not very significant.

Tablet compactability. Tablet compactability was very similar at lower compression forces (<15 kN), but at higher compression forces, both HPC-SSL SFP and HPC-SL FP demonstrated better results (Figure 7). Though the difference in MW between SL FP and L FP is only 40,000 daltons (perhaps not intuitively a large difference), the L FP grade produced tablets with the lowest breaking force when compressed at pressures exceeding 15 kN.

Tablet disintegration. Figure 8 lists the tablet disintegration times. Paradoxically, the fastest disintegration was observed with the highest-MW (highest-viscosity) HPC, which was L FP. This interesting result can be explained by the hydration rate of the different HPC grades. The factor correlated to disintegration in high-shear granulation is obviously not the equilibrium viscosity (polymer MW), but the speed with which this viscosity is generated. Due to its low MW and micronized particles, SSL SFP hydrates much faster than the other grades. This rapid development of viscosity inside the tablet can decrease the water uptake. Despite the fact that SSL SFP equilibrium viscosity is the lowest among the three tested HPC grades, it is generated more
Tablet friability. All the tablets showed acceptable friability results (Figure 9). No impact of the HPC’s MW was observed.

Conclusions: High-shear granulation. From these results, the following conclusions can be drawn regarding high-shear granulation:

The HPC’s MW has a minor effect on the granules’ PSDs. Slightly fewer fines were created with HPC-SSL SFP;

The lower MW HPCs (SSL and SL) have better compactability at higher compression forces (>15 kN); and

Tablet disintegration time is inversely correlated to the HPC’s MW: The higher the MW, the faster the disintegration, which is counterintuitive and the opposite of the results observed in the fluid-bed granulation that used a dissolved binder. For high-shear granulation, disintegration time ranks thusly: L FP < SL FP < SSL SFP.

Comparison: Fluid-bed versus high-shear granulation

PSD of the granules. A comparison of the PSDs of granules prepared using these wet granulation methods appears in Figure 10.

As the figure shows, fluid-bed granulation produced finer particles and a narrower PSD. The difference is most prominent at the lowest-MW HPC (SSL), followed by SL and L. This implies a strong MW dependence: The higher the MW, the smaller the difference between the granule PSDs obtained from both granulation techniques. The coarser granules resulting from high-shear granulation demonstrated better powder flow across all three HPC grades (Figure 11).
Powder compactability. The tablet compaction properties of the granules produced by fluid-bed granulation were much better than those produced by high-shear granulation (Figure 12). At a given compression force and HPC MW, the tablet breaking force was between 30% and 90% higher when a dissolved binder is used (fluid-bed granulation). This is likely due to the finer and more homogeneous particle size of granules produced by the fluid-bed method.

Tablet disintegration. At a given MW, the disintegration time of tablets made from the high-shear granulations was much faster than that of tablets made from the fluid-bed granulations (Figure 13). This could be related to the more fragile nature of the granules made by the high-shear method (dry binder). They are more fragile because the bridges between the particles are not as strong as those made using a dissolved binder. This fragility is thought to facilitate tablet disintegration.

Tablet friability. Tablet friability was acceptable for all formulations (Figure 14), with no significant dependence on MW or granulation method.

Conclusions: Fluid-bed versus high-shear granulation. When comparing granulations with the same MW of HPC:

- Fluid-bed granulation produced smaller granules with narrower PSDs and better tablet compaction;
- High-shear granulation produced larger granules with broader PSDs and better flow properties;
- With fluid-bed granulation, disintegration times are shorter, and the lower the MW of the HPC, the faster the disintegration: SSL < SL < L;
- With high-shear granulation, the higher the MW of the HPC, the faster the disintegration: L < SL < SSL; and
- No significant differences in tablet friability were observed.

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