Guidance Document
for Processing Carbopol®
in Oral Solid Dosage Forms
Guidance Document for Processing Carbopol® in Oral Solid-Dosage Forms

Lubrizol LifeSciences combines an in-depth understanding of functional polymer systems with a portfolio of specialty materials to deliver application-specific solutions to the medical device, pharmaceutical and healthcare industries. As a technology leader and a key provider of pharmaceutical polymers, LifeSciences is your custom solution development partner. Together, we help link science to life.

Our polymers are highly efficient gel matrix-formers for controlling drug release in tablets, capsules and multiparticulate systems. In many cases, our polymers have demonstrated slower drug-release rates at lower concentrations than other commercially available excipients, enabling overall formulation cost savings and smaller tablet sizes. Additionally, tablet formulations using Carbopol has demonstrated excellent physical properties such as hardness and low friability over a wide range of compression forces.

Carbopol is widely compatible with commonly used pharmaceutical ingredients and can be used alone or in combination with other extended-release excipients to achieve a desired release profile. Carbopol is available in both powder and granular forms, therefore they can be used in all types of tablet and capsule manufacturing processes.

1. Availability of powder and granular grades allows manufacturing by different types of technology (e.g., direct compression and granulation)

2. Powder and granular Carbopol grades can be combined in a formulation

3. Carbopol can be used part intragranularly and part extragranularly in a formulation

Carbopol enables processing versatility in order to achieve targeted drug-release profiles.

- Aqueous granulation
- Non aqueous granulation
- Dry granulation

Powder grades of Carbopol are more efficient in extending drug release than the granular grade; however, the powder grades are not free-flowing. As a general rule, the methods which are most efficient for the powder grades in extending drug release are:

- Aqueous granulation
- Non aqueous granulation
- Dry granulation

Carbopol can be used alone or in combination with other extended-release excipients such as hypromellose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polyethylene oxide, sodium alginate and methacrylic polymers. The combination allows for flexibility in achieving various release profiles. Additionally, lower total polymer levels may be needed compared to using a single polymer, thus enabling overall cost savings and smaller tablet sizes.

Low polymer levels (1%–3%) can be used in conventional formulations (immediate-release) to provide binding properties. The polymers can be incorporated by direct compression or wet granulation (preferably by adding to the dry powder blend or by spraying as a dispersion in water or solvents).

For all processes, conditions should be controlled (low relative humidity) to address the hygroscopicity of the polymer. Selection of container/closure system is critical for product stability (moisture permeation).
## Formulation and Processing Considerations

### Method of Tablet Manufacture

<table>
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<tr>
<th>Method of Tablet Manufacture</th>
<th>Recommended Grade</th>
<th>Typical Polymer Levels</th>
<th>Formulation/Processing Considerations</th>
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</thead>
<tbody>
<tr>
<td><strong>Direct Compression</strong></td>
<td>Carbopol® 71G NF</td>
<td>10–30%</td>
<td>• Carbopol has good binding properties (compressibility). Powder grades have very fine particle size and static charge (thus not free-flowing).&lt;br&gt;• Carbopol 71G NF is in granular form and has good flowability. Therefore, it can be processed easier than the powder Carbopol.&lt;br&gt;• Powder grades of Carbopol are more efficient in extending drug release than the granular grade due to the larger surface area, thus lower levels of polymer are generally needed.&lt;br&gt;• Carbopol 71G NF can be added to improve the flow properties of the formulation.&lt;br&gt;• Varying the compression forces to achieve acceptable hardness generally does not significantly affect the drug-release characteristics.&lt;br&gt;• An important consideration is that segregation may occur in the powder blend. Segregation might be prevented by preblending the active pharmaceutical ingredient (API) and polymers using ingredients with similar particle size distribution and density or by achieving ordered mixing.&lt;br&gt;• APIs with poor flowability or compressibility can be granulated and the granules blended with Carbopol.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 974P NF</td>
<td>3–5%</td>
<td></td>
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<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>3–5%</td>
<td></td>
</tr>
<tr>
<td><strong>Nonaqueous Granulation</strong></td>
<td>Carbopol® 974P NF</td>
<td>5–25%</td>
<td>• The advantage of using Carbopol in nonaqueous solvents is to avoid rapid swelling of the polymer, which facilitates processing.&lt;br&gt;• Nonaqueous granulation is possible at Carbopol levels greater than 10% of the blend, when aqueous granulation is difficult.&lt;br&gt;• Ethanol and isopropyl alcohol can be used as granulating solvents. The swelling of Carbopol is faster in ethanol than in isopropyl alcohol.&lt;br&gt;• It is important to avoid contact with water and moisture (control relative humidity, use dry equipment).</td>
</tr>
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<td></td>
</tr>
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<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>5–25%</td>
<td></td>
</tr>
<tr>
<td><strong>Aqueous Granulation (High/low shear)</strong></td>
<td>Carbopol® 974P NF</td>
<td>5–10%</td>
<td>• Controlled release can be efficiently achieved at low levels (5%–10%) due to the large surface area of the powder-grade polymer.&lt;br&gt;• Generally, it is recommended to incorporate the polymer in the powder blend (versus adding it as a dispersion in water) due to the high viscosity of the polymer.&lt;br&gt;• Screening or combing the polymer with other ingredients is beneficial to improve dry polymer handling (compensates for static charge and fine particle size).&lt;br&gt;• No additional binder is required because Carbopol has good binding properties.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 971P NF</td>
<td>5–10%</td>
<td>• Incorporation of microcrystalline cellulose improves the processability of the formulation. Generally, less than 10% of microcrystalline cellulose should be used to prevent disintegration of the tablets.&lt;br&gt;• In order to avoid fast and extensive swelling of the polymer, add a low amount of granulation liquid sprayed at a slow rate in fine droplets (uniform distribution of the water in the wet mass).&lt;br&gt;• Granulation should be controlled in order to prevent overwetting (sticky, rubbery mass).&lt;br&gt;• The amount of granulation liquid used is typically lower than that expected for cellulose polymers.</td>
</tr>
<tr>
<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>5–10%</td>
<td>• It is very important to control the drying process and residual moisture in the granules (typical values 1%–3%); however, these parameters are formulation-specific. If overdried, Carbopol forms hard granules. High residual moisture might lead to tablets sticking to the punches and stability problems.&lt;br&gt;• Varying the compression forces to achieve acceptable hardness generally does not significantly affect the drug-release characteristics.</td>
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<td><strong>Fluid Bed Granulation</strong></td>
<td>Carbopol® 974P NF</td>
<td>5–10%</td>
<td>• Carbopol has small particle size, static charge and low density, therefore precautions need to be taken during granulation.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 971P NF</td>
<td>5–10%</td>
<td>• The fluidization should be kept low at the beginning of the process to prevent adherence of Carbopol to the filter bag.</td>
</tr>
<tr>
<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>5–10%</td>
<td>• The spray rate should be controlled to prevent formation of large, overwet agglomerates.</td>
</tr>
<tr>
<td><strong>Dry Granulation (roller compaction)</strong></td>
<td>Carbopol® 974P NF</td>
<td>3–20%</td>
<td>• Roller compaction avoids rapid polymer swelling in water.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 971P NF</td>
<td>3–20%</td>
<td>• It is recommended to blend all of the ingredients except the lubricant prior to compaction to achieve slower release rates.</td>
</tr>
<tr>
<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>3–20%</td>
<td>• The formulation does not need an additional binder when Carbopol is included. For example, Carbopol 71G NF is currently manufactured by roller compaction of Carbopol 971P NF with no additional additives.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 974 NF</td>
<td>5–20%</td>
<td>• The polymer properties are not affected by multiple compaction steps.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 971P NF</td>
<td>5–20%</td>
<td>• Carbopol must be used with microcrystalline cellulose in order to reduce the tackiness of the wet mass and facilitate processing.</td>
</tr>
<tr>
<td></td>
<td>Noveon® AA-1 Polycarbophil</td>
<td>5–20%</td>
<td>• Extrusion spheronization using water is possible and recommended versus a solution of electrolytes. The amount of water, extrusion speed, spheronization speed and time need to be optimized in order to obtain the highest yields and sphericities.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 974P NF</td>
<td>5–50%</td>
<td>• In the presence of electrolytes (e.g., calcium chloride), the processing is easier, but the electrolyte has a negative consequence on the bioadhesion and drug release.</td>
</tr>
<tr>
<td><strong>Hot Melt Extrusion</strong></td>
<td>Carbopol® 974P NF</td>
<td>5–50%</td>
<td>• Carbopol can be used in combination with thermoplastic materials.</td>
</tr>
<tr>
<td></td>
<td>Carbopol® 971P NF</td>
<td>5–50%</td>
<td>• The method is also suitable to obtain solid dispersion of low-solubility APIs.</td>
</tr>
</tbody>
</table>

### Direct Compression Procedure

**1. Screening**
Weigh all ingredients except the lubricant and screen them (20–45 mesh screen). Add the low-density material first and the high-density material at the end.

It is beneficial to combine materials with poor flowability, small particle size or static charge with another material in order to improve the overall handling of the powder blend. For example, it is recommended to combine powder grade Carbopol with some fillers or combine an API with Carbopol 71G NF.

Note: Sometimes a pre-blending step is done to facilitate screening.

**2. Mixing**
Mix the powder blend to achieve content uniformity. Add the lubricant to the powder blend and mix for 2–5 minutes (avoid overmixing and overlubrication).

**3. Compression**
Compress the powder blend to target weight and hardness.
Wet Granulation Procedure

1. Milling/Sieving
Weigh all ingredients except the lubricant and screen/mill them (20–45 mesh). Add the low-density material first and the high-density material at the end.

It is beneficial to combine materials with poor flowability, small particle size or static charge with another material in order to improve the overall handling of the powder blend. For example, it is recommended to combine powder-grade Carbopol with some fillers.

Note: Sometimes a pre-blending step is done to facilitate screening.

2. Dry Blending (low/high shear granulators)
Mix the powder blend to achieve content uniformity.

3. Preparation of the Liquid Binder (agglutinant)
This step is not generally necessary as Carbopol can be granulated with deionized water or solvents (no additional binder needed).

4. Wet Massing (low/high shear granulators)
Granulate the powder blend with deionized water or solvents. In order to avoid fast and extensive swelling of the polymer, use a low amount of granulation liquid added at a slow rate in fine droplets (uniform distribution of the water in the wet mass). Granulation should be controlled in order to prevent overwetting (sticky, rubbery mass). Incorporation of microcrystalline cellulose improves the processability of the formulation. Generally, less than 10% of microcrystalline cellulose should be used to prevent disintegration of the tablets.

5. Wet Screening
Pass the wet mass through a screen (6–12 mesh).

6. Drying of the Granules
Dry the granules in an oven or in a fluid bed dryer until residual moisture is approximately 1.5%. If overdried, Carbopol forms hard granules. High residual moisture might lead to tablets sticking to the punches and stability problems.

7. Screening of the Granules
Pass the granules through a screen (16–20 mesh) to break down any agglomerates formed during drying.

8. Mixing of the Granules with Extragranular Components
Add the lubricant to the granules and mix for 2–5 minutes (avoid overmixing and overlubrication).

9. Compression
Compress the granules to the target weight and hardness.

Dry Granulation Procedure (Roller Compaction)

1. Milling/Sieving
Weigh all ingredients except the lubricant and screen/mill them (20–45 mesh). Add the low-density material first and the high-density material at the end.

2. Mixing
Mix the powder blend to achieve content uniformity.

3. Compaction
Compact the powder blends and control the process parameters (feed rate, compaction pressure, roll speed, roll gap).

4. Sizing
Size the ribbon to the target particle size. If necessary, recycle the over-and under-sized-material.

5. Mixing With Extragranular Components
Add the lubricant to the granules and mix for 2–5 minutes (avoid overmixing and overlubrication).

6. Compression
Compress the granules to the target weight and hardness.
Equipment Cleaning Recommendations

- Manufacturing equipment should be promptly cleaned after processing carbomer dispersions.
- Gelled residue may be removed by power washing with warm water.
- If an excessive gel layer has formed, it may be collapsed using a dilute solution of salt (5% w/v).
- Any dry residue that remains on equipment after processing may be soaked for 10–30 minutes using warm (~65ºC) dilute alkaline solutions and then removed with pressure washing.

Recommended detergent solutions:

- 2% solution of P3-cosa® CIP 95 (Ecolab GmbH & Co. OHG)
- 0.2% solution of Extran® AP12 (EMD-Merck KGaA)

Technical References

Direct Compression

- Dosage form of N-acetyl cysteine, United States Patent 6623754.

Nonaqueous Granulation


Aqueous Granulation


• Controlled-release solid dosage carbamazepine formulations, United States Patent 6572889.

• Controlled-release solid-dosage nifedipine formulations, United States Patent 20040219210

**Fluid Bed Granulation**


• Controlled-release pharmaceutical compositions for the oral administration containing nifedipine as active substance, United States Patent 5871775.

**Dry Granulation (Roller Compaction)**


• Controlled-release polycrylic acid granules and a process for preparing the same, United States Patent 9792267.

• Method of stabilizing bupropion hydrochloride tablets, European patent EP 1499301.

**Extrusion Spheronization**


**Hot Melt Extrusion**


• Free-flowing granules containing carbomer, United States Patent 20070048364.
The Lubrizol Advantage

Lubrizol LifeSciences is a healthcare solution partner that provides customer support from idea to execution by supplying customizable polymers and excipients, complex drug formulation development and best-in-class contract manufacturing services for medical device and pharmaceutical manufacturers.