Application Studies of L-HPC and HPMCAS for Pharmaceutical Dosage Forms
- Update -

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L-HPC

1) Application to a Proton-Pump Inhibitor Formulation

2) Application to Orally-Disintegrating Tablets

HPMCAS

3) Effect of Succinoyl/Acetyl Substitution on Drug Dissolution from Solid Dispersion Prepared by Melt-Extrusion

Low-Substituted Hydroxypropyl Cellulose

L-HPC
Functions of L-HPC

- Disintegrant
- Dry Binder
- Anti-Capping Agent
- Others

\[
\begin{align*}
\text{R} & = \text{H} \\
\text{CH}_2\text{CH(OH)}\text{CH}_3
\end{align*}
\]

Manufacturing Process of L-HPC

1. NaOH
2. Pulp
3. Propylene oxide
4. Alkali cellulose
5. Reaction
6. Drying
7. Washing
8. Precipitation
9. Milling
10. Product
L-HPC vs HPC

L-HPC (Insoluble in water)
Molar substitution* = 0.2

HPC (Soluble in water)
Molar substitution = 3.5

CAS No : 9004-64-2

Grades of L-HPC

LH-11
“Fibrous”
app. 50 μm
L/D:5.0
Best for
Anti-Capping

LH-21
“Regular”
app. 40 μm
L/D:3.8

LH-31
“Micronized”
app. 20 μm
L/D:3.6
Best for
Pellet Extrusion

LH-B1
“Non-Fibrous”
app. 50 μm
L/D:2.5
Development History

LH-11
1977

LH-21
1980's

LH-31

LH-B1
2002

NBD
2011

Variety of Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Particle appearance</th>
<th>Description</th>
<th>Mean particle size (mm)</th>
<th>Bulk density (g/mL)</th>
<th>Tap density (g/mL)</th>
<th>Aspect ratio</th>
<th>Angle of repose (°)</th>
<th>Hydroxy-propoxy content (%)</th>
<th>Average molecular weight</th>
<th>Typical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-11</td>
<td>Most fibrous</td>
<td></td>
<td>50</td>
<td>0.34</td>
<td>0.57</td>
<td>5.0</td>
<td>49</td>
<td>11</td>
<td>130,000</td>
<td>Direct compression (anti-capping)</td>
</tr>
<tr>
<td>LH-21</td>
<td>Moderately fibrous</td>
<td></td>
<td>40</td>
<td>0.40</td>
<td>0.65</td>
<td>3.8</td>
<td>45</td>
<td>11</td>
<td>120,000</td>
<td>Regular grade (dry mixing, wet granulation)</td>
</tr>
<tr>
<td>LH-22</td>
<td>Moderately fibrous/ low hydroxypropoxyl</td>
<td></td>
<td>40</td>
<td>0.37</td>
<td>0.63</td>
<td>3.8</td>
<td>48</td>
<td>11</td>
<td>135,000</td>
<td>Lower hydroxypropoxyl than LH-21 (sometimes better disintegration)</td>
</tr>
<tr>
<td>LH-31</td>
<td>Micronized</td>
<td></td>
<td>20</td>
<td>0.30</td>
<td>0.59</td>
<td>3.6</td>
<td>49</td>
<td>11</td>
<td>100,000</td>
<td>Pellet extrusion, Layering</td>
</tr>
<tr>
<td>LH-32</td>
<td>Micronized/ low hydroxypropoxyl</td>
<td></td>
<td>20</td>
<td>0.21</td>
<td>0.49</td>
<td>3.6</td>
<td>53</td>
<td>8</td>
<td>115,000</td>
<td>Pellet extrusion, layering (sometimes better disintegration than LH-31)</td>
</tr>
<tr>
<td>LH-81</td>
<td>Non fibrous</td>
<td></td>
<td>50</td>
<td>0.50</td>
<td>0.70</td>
<td>2.5</td>
<td>40</td>
<td>11</td>
<td>140,000</td>
<td>Fluid-bed granulation, direct compression for high-load formulations</td>
</tr>
</tbody>
</table>

Nomenclature

<table>
<thead>
<tr>
<th>LH</th>
<th>Particle identification</th>
<th>Chemical identification (Substituent level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coarse</td>
<td>1: High (11%)</td>
</tr>
<tr>
<td>2</td>
<td>Medium</td>
<td>2: Low (8%)</td>
</tr>
<tr>
<td>3</td>
<td>Micronized</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>High bulk density</td>
<td></td>
</tr>
</tbody>
</table>
Application to a Proton-Pump Inhibitor Formulation (Drug-Layered Beads)

Lansoprazole (proton-pump inhibitor)

- Unstable under acidic conditions (Best stability at pH 9)
- Enteric coating is necessary.
- Interactive to excipients
- Stabilizer is necessary (CaCO$_3$ was found to be the best).
Extrusion Method

CF Method

FIGURE 1.
Methods for manufacturing core granules.

Tabata et al., Drug Dev. Ind. Pham. 20, 1661 (1994)

Extrusion Method

CF Method

FIGURE 2.
Effect of the manufacturing method on the stability of lansoprazole in enteric granules in capsules stored at 40°C.
- ○ -, % of initial; □, ΔE of the granules in the capsules.

Tabata et al., Drug Dev. Ind. Pham. 20, 1661 (1994)
Table 1. Formulation of Lansoprazole-Coated Microgranules

<table>
<thead>
<tr>
<th>Layer</th>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>Lactose monohydrate–microcrystalline cellulose spheres</td>
<td>30 mg</td>
</tr>
<tr>
<td>Active compound layer</td>
<td>Lansoprazole</td>
<td>30 mg</td>
</tr>
<tr>
<td></td>
<td>Magnesium carbonate</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Low-substituted hydroxypropyl cellulose (LH-32)</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>Hydroxypropyl cellulose</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Purified water&lt;sup&gt;a)&lt;/sup&gt;</td>
<td>128 μl</td>
</tr>
<tr>
<td>Intermediate layer</td>
<td>Hydroxypropyl methycellulose 2910</td>
<td>9.5 mg</td>
</tr>
<tr>
<td></td>
<td>Other&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>0.5 mg</td>
</tr>
<tr>
<td></td>
<td>Purified water&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>40 μl</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>95 mg</td>
</tr>
</tbody>
</table>

<sup>a)</sup> Removed during processing.  
<sup>b)</sup> Low-substituted hydroxypropyl cellulose (LH-32) and/or talc.


Benefits of L-HPC (LH-32)
in the Lansoprazole-Layered Beads

- Reduces friability, without delaying disintegration.
- Minimal Interaction with API.
Application of L-HPC - *NBD Grade* - to Orally Disintegrating Tablets

### L-HPC NBD-Grades

<table>
<thead>
<tr>
<th>Feature</th>
<th>New grade</th>
<th>Conventional grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NBD-022</td>
<td>NBD-021</td>
</tr>
<tr>
<td>Hydroxypropoxy (%)</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>D₅₀ (μm)</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>D₉₀ (μm)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>D₉₀/D₅₀</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>Feature</th>
<th>Typical application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quick swelling</td>
<td>For Orally Disintegrating Tablets (ODT)</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>For Direct Compression (DC)</td>
</tr>
<tr>
<td></td>
<td>Higher binding capability</td>
<td>For Wet Granulation (WG)</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td></td>
</tr>
</tbody>
</table>

The data is typical value and not specification.
NBD Grades: Compared to the Regular Grades

- **Flowability:** Non Fibrous = Better
- **Compressibility:** Better
- **Disintegration:** Same

**Wicking Test**

Flat-faced Tablet 150 mg/T  
Compression Pressure 70MPa  
Purified Water + Pigment
Suspension Viscosity

Viscosity $\propto$ Mouth feel

Advantages of NBD-022

- Faster disintegration
- Good flowability
- Good mouth feeling
- Good API dissolution
- Excellent stability

→ Good For Orally Disintegrating Tablets (ODT)
Mannitol Tablets (DC Method)

Ingredient Weight Ratio

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol (Granulated)</td>
<td>85</td>
</tr>
<tr>
<td>L-HPC (NBD-022, or LH-21)</td>
<td>15</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>1</td>
</tr>
</tbody>
</table>

Tablet Weight 250 mg
Diameter 8 mm
VERGO® Rotary Tableting Machine (Kikusui, Japan)
Wet Granulation by Spraying L-HPC Suspension

Equipment: Multiplex MP-01 (Powrex, Japan)
Inlet Temperature: 60°C
Outlet Temperature: 27-28°C
Inlet Air Flow: 0.45-0.6 m³/min
Spray Rate: 12 g/min
Atomizing Pressure: 150 kPa
Post Drying: Until 45°C-outlet

6% L-HPC suspended in water

 Tablets from Wet Granulation by Spraying L-HPC Suspension

(Mannitol / L-HPC / Mg stearate = 100 / 6 / 0.5)
Hypromellose Acetate Succinate NF

Hydroxypropylmethylcellulose Acetate Succinate JPE

HPMCAS

Shin-Etsu AQOAT®

Cellulose, 2-hydroxypropyl methyl ether, acetate, hydrogen butanedioate
CAS registry number 71138-97-1

R = -H, -CH₃, -CH₂CH(CH₃)OH, -COCH₃, -COCH₂CH₂COOH
Structure

HPMC

HPMCP

HPMCAS

: Methyl
: Hydroxypropyl
: Phthalyl
: Succinoyl
: Acetyl

Commercial APIs using HPMCAS

- ATP sodium
- Bisacodyl
- Cefaclor
- Cefalexin
- Diclofenac sodium
- Diltiazem HCl
- Docaparmine HCl
- Duloxetine HCl
- Efonidipine HCl
- Fluoxetine HCl
- Ivacaftor
- Kallidinogenase
- Nicardipine HCl
- Omeprazole
- Pancreatin
- Salazosulfapyridine
- Telaprevir
- Vemurafenib
Compendial Status of HPMCAS

• Hypromellose Acetate Succinate NF

• Hydroxypropylmethylcellulose Acetate Succinate JPE
  → Hypromellose Acetate Succinate JP
  (In Processing)

Effect of Succinoyl and Acetyl Substitutions in HPMCAS on Dissolution Profile of Nifedipine Solid-Dispersion Prepared by Melt Extrusion
Preparation of HPMCAS Samples (Various Succinoyl/Acetyl Content)

Characterization
Chemical Analysis (NF-Monograph)
Tg (DSC)
Surface Tension of solution in pH 6.8 Phosphate Buffer by Ring Method
Solubility Parameter ($\delta$) calculated by Fedor’s method

Nifedipine – HPMCAS (1 : 2) Melt-Extrusion
Capillary Rheometer (Capilograph®, Toyoseiki, Japan)
170-180°C, 50 mm/min, 1 mm-d

Dissolution Test / pH 6.8 (100 rpm)

Characteristics of Prepared HPMCAS Samples

<table>
<thead>
<tr>
<th>Grade</th>
<th>AS-L</th>
<th>AS-M</th>
<th>AS-H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Sample ID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>mPa-s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxy</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropoxy</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinoyl</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetyl</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tg / DSC</td>
<td>ºC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta$ _Fedor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta \delta$ _Fedor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface Tension</td>
<td>dyne/cm²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.2</td>
<td>44.6</td>
<td>44.2</td>
<td>45.2</td>
<td>43.7</td>
<td>40.7</td>
<td>40.4</td>
<td>40.2</td>
<td></td>
</tr>
</tbody>
</table>

* Nifedipine = 22.91
Dissolution Profiles of Nifedipine

*The original solubility of Nifedipine is 12 mg/L

Inhibition of Recrystallization vs Solubility Parameter and Surface Tension
• Substitution level of succinoyl and acetyl groups in HPMCAS influenced the dissolution of Nifedipine.

• There was an optimum range of substitution to achieve a good dissolution and maintaining supersaturation.

• Surface tension and solubility parameter were correlated to the substitution level and they may be related to dissolution.