Shin-Etsu

Low-Substituted Hydroxypropyl Cellulose NF

# L-HPC

Functional Disintegrant

## CONTENTS

# Introduction

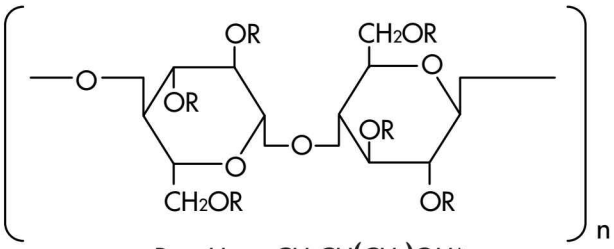
**L-HPC** (Low-Substituted Hydroxypropyl Cellulose) was first approved in 1977 as a disintegrant for pharmaceutical dosage forms in Japan. In addition to the conventional LH grades, NBD grades which have improved flowability and compressibility were newly introduced in 2011.
A recent survey shows that **L-HPC** is ranked as the first choice of tablet disintegrant by Japanese pharmaceutical companies.

The key benefits of **L-HPC** include:

- Higher stability due to its non-ionic nature and low water activity
- No peroxide offers superior stability
- Disintegration into smaller particles leading to better dissolution
- Anti-capping effect for tableting process
- Suitable for pellet extrusion as well as tableting
- A variety of grades are available depending on application

This brochure briefly describes the properties of **L-HPC**.
If you are interested in its characteristics and application, or have any questions, please contact us for further information.

# Description

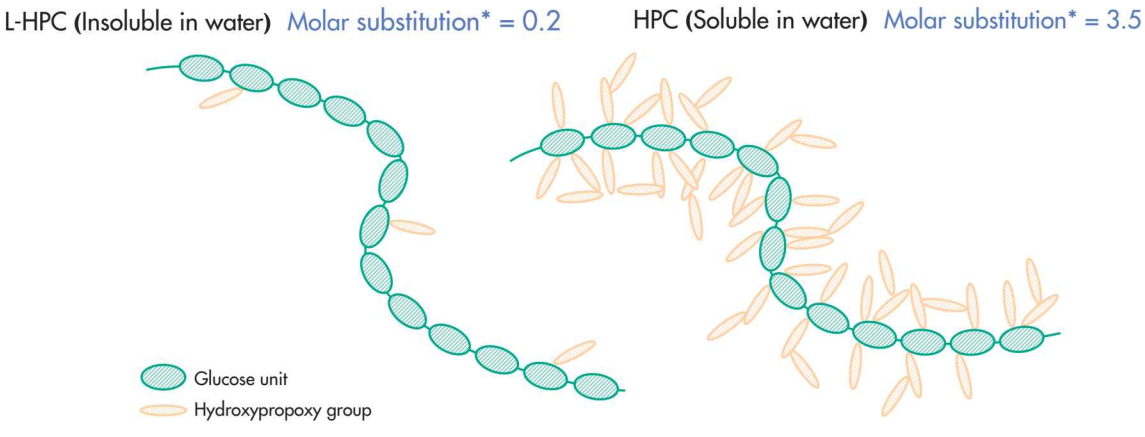
| | |
|---|---|
| Trade name | L-HPC |
| Generic name | Low-substituted hydroxypropyl cellulose |
| Abbreviation | L-HPC |
| IUPAC name | Cellulose, 2-hydroxypropyl ether (low substituted) |
| CAS RN® | 9004-64-2 |
| Compendial status | NF (US National Formulary)<br>EP (European Pharmacopoeia)<br>JP (Japanese Pharmacopoeia)<br>21 CFR 172.870 (Code of Federal Register / Food Additive) |
| Structure |  <br><br>R = -H or -$CH_2CH(CH_3)OH$* |

*A $^{13}$C-NMR study has shown that most hydroxypropoxy groups are attached via glucopyranose position 6 (Alvarez-Lorenzo *et al.*, 2000).

## ◆ L-HPC vs. HPC

L-HPC is NOT the same as HPC. Although sharing the same CAS number, L-HPC has different characteristics from Hydroxypropylcellulose (HPC), a binding agent widely used for solid dosage forms. L-HPC and HPC have separate monographs in pharmacopoeias. While the regular HPC has a large amount of hydroxypropoxy groups in the cellulose backbone, L-HPC has only a small level (See the picture below). Due to this chemical difference, HPC is soluble in water, but L-HPC is insoluble. HPC is typically used for a granulation binder in an aqueous solution, but L-HPC cannot be used in this way. L-HPC is an effective disintegrant due to its swelling action in water, but this is not the case with HPC.

Because L-HPC also has good compressibility, dry blending of this material produces hard tablets similar to those made from microcrystalline cellulose. In this application, L-HPC functions as a "dry binder."

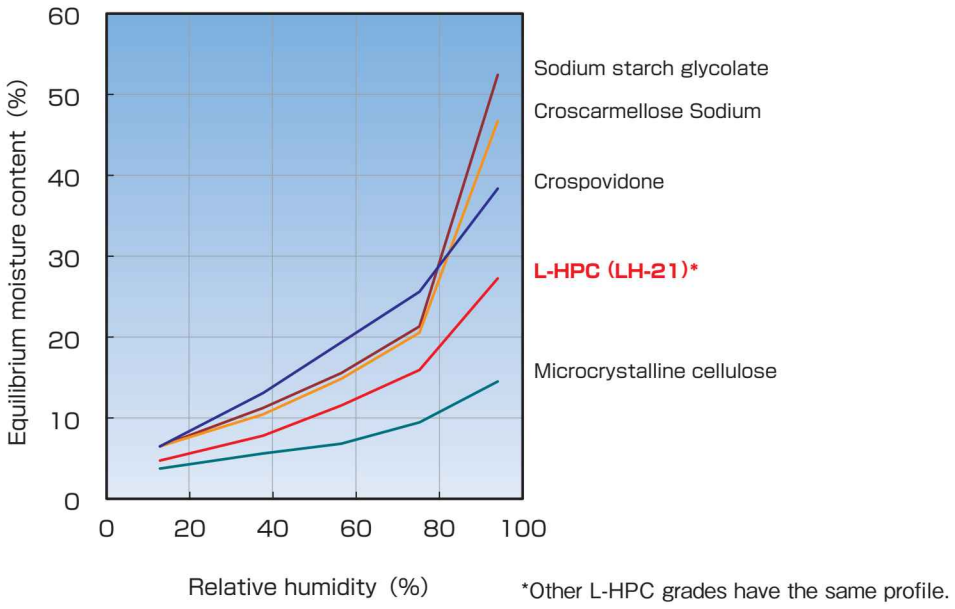



* Average number of hydroxypropoxy groups per glucose unit

# General Properties

| | |
|---|---|
| Appearance | White to yellowish-white powder |
| True density | 1.3 g/cm$^3$ (measured with helium pycnometer) |
| Solubility | Not soluble in water or practical organic solvents.<br>Swells in water.<br>Soluble in 10 % NaOHaq., as a viscous and turbid solution. |
| Thermal degradation temperature | approx. 290 ℃ |

Equilibrium moisture content (25 ℃ )




*Other L-HPC grades have the same profile.

Water-Soluble Substances

| | 25℃ | 50℃ (%) |
|---|---|---|
| Sodium starch glycolate | 10 | 12 |
| Croscarmellose Sodium | 2.0 | 6.5 |
| Crospovidone | 0.8 | 1.3 |
| L-HPC | 1.9 | 1.8 |
| Microcrystalline cellulose | 0.4 | 0.5 |

## Manufacturing

The raw material of L-HPC is highly-purified wood pulp.
L-HPC is manufactured under GMP* (Good Manufacturing Practices).

* Self-established excipient GMP based on the guideline proposed by IPEC (International Pharmaceutical Excipient Council)

**Pulp**
(Pure cellulose)

**Mercerization Process**

**Etherification Process**

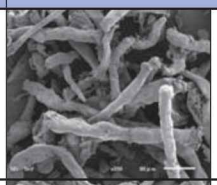
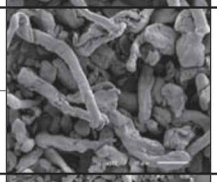
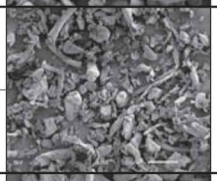
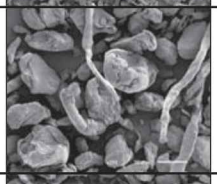
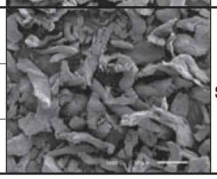
**Purification Process**

**Drying Process**

**Milling Process**

**L-HPC**

## Variety of Grades

| Grade | Particle attribute | |
|---|---|---|
| LH-11 |  | Most fibrous |
| LH-21 |  | Moderately fibrous |
| LH-22 | | |
| LH-31 |  | Micronized |
| LH-32 | | |
| LH-B1 |  | Non fibrous |
| NBD-020 |  | short particle |
| NBD-021 | | |
| NBD-022 | | |

Currently nine grades are commercially available. They have different particle sizes/shapes and chemical substitution levels. The numbers have variations depending on lot, grade, and determined method. See the following table. The following data shows only typical and approximate values. These are not specifications.
For specification, see page 17 of this brochure.

| Mean particle size(D50)μm | 90% cumulative particle size(D90)μm | D90/D50 | Bulk density (g/mL) | Tapped density (g/mL) | Aspect ratio | Angle of repose(°) | Hydroxypropoxy content (%) | Typical application |
|---|---|---|---|---|---|---|---|---|
| 50 | 180 | 3.6 | 0.33 | 0.56 | 5 | 48 | 11 | Direct compression (anti-capping) |
| 45 | 135 | 3.0 | 0.38 | 0.63 | 3.8 | 45 | 11 | (Standard grade) Direct compression, wet granulation |
| 45 | 135 | 3.0 | 0.37 | 0.63 | 3.8 | 46 | 8 | Direct compression, wet granulation |
| 20 | 80 | 4.0 | 0.28 | 0.59 | 3.6 | 49 | 11 | Wet granulation, pellet extrusion, layering |
| 20 | 80 | 4.0 | 0.21 | 0.55 | 3.6 | 50 | 8 | Wet granulation, pellet extrusion, layering |
| 50 | 125 | 2.5 | 0.48 | 0.70 | 2.5 | 40 | 11 | Direct compression, fluidized bed granulation |
| 45 | 100 | 2.2 | 0.32 | 0.52 | 2.2 | 43 | 14 | Wet granulation |
| 45 | 100 | 2.2 | 0.32 | 0.52 | 2.2 | 43 | 11 | Direct compression, wet granulation |
| 45 | 100 | 2.2 | 0.32 | 0.52 | 2.2 | 43 | 8 | Direct compression, ODTs |

## ◆ Nomenclature

**LH-NBD-021**

Particle identification

1: Coarse
2: Medium size
3: Micronized
B: High bulk density

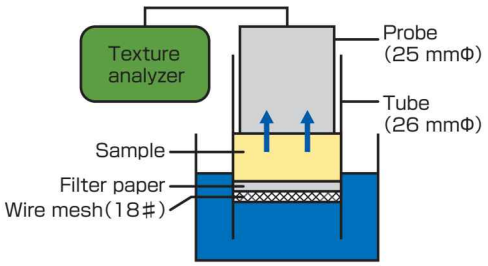
Chemical identification (hydroxypropoxy level)

0: High (14 %)
1: Standard (11 %)
2: Low (8 %)

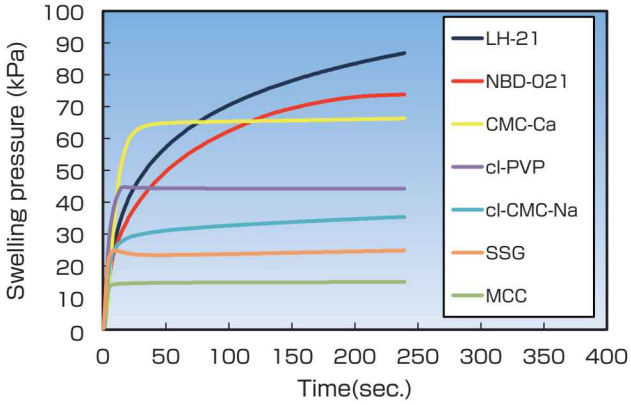
# Swelling Property

L-HPC is not soluble in water. However it absorbs water and significantly expands the volume. This swelling action causes tablets to quickly disintegrate. The swelling volume is dependent on particle size and hydroxypropoxy content, as shown below. This experiment was carried out using the texture analyzer as shown on the right. Swelling pressure was detected when 1 g of sample absorb the water from the bottom.

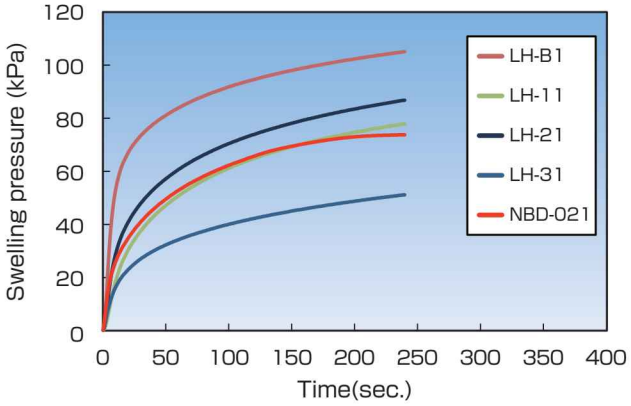
Compared to other excipients, L-HPC swells and reaches its maximum volume quicker.



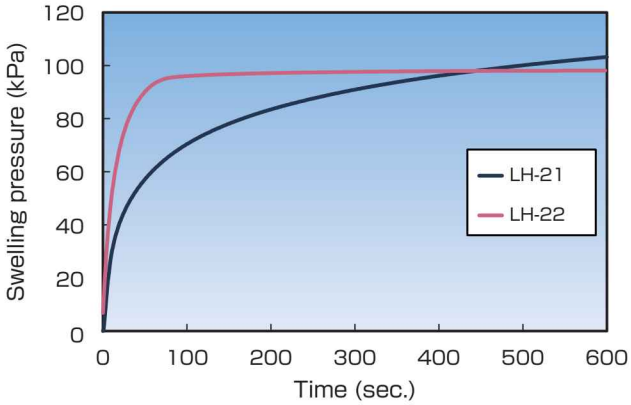

**Comparison with other excipients**



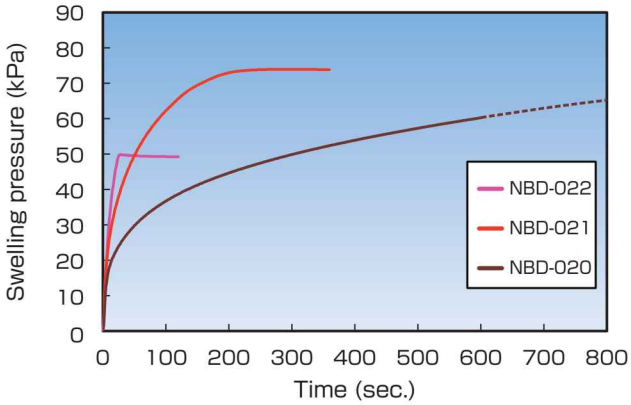

**Effect of particle size**




**Effect of hydroxypropoxy content**



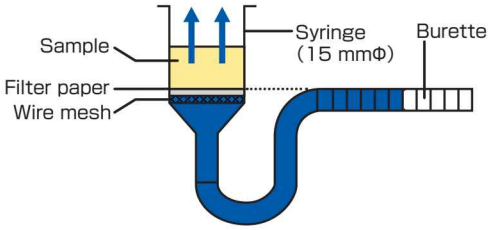

**Effect of hydroxypropoxy content**

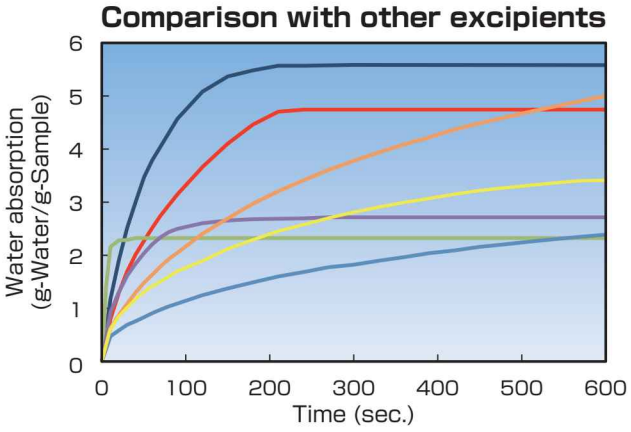


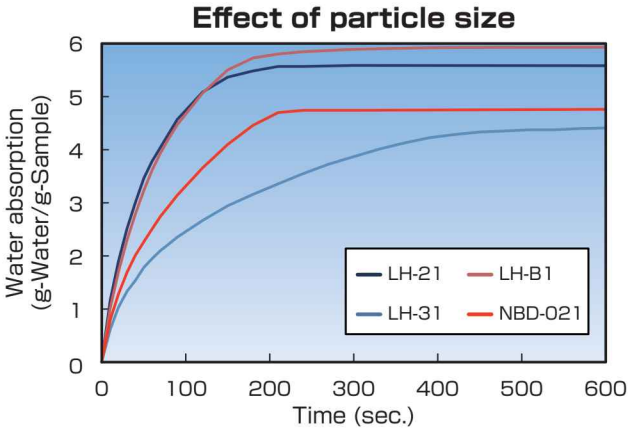

cl-CMC-Na: Croscarmellose sodium
cl-PVP: Crospovidone
SSG: Sodium starch glycolate
MCC: Microcrystalline cellulose PH-101
CMC-Ca: Carmellose Calcium

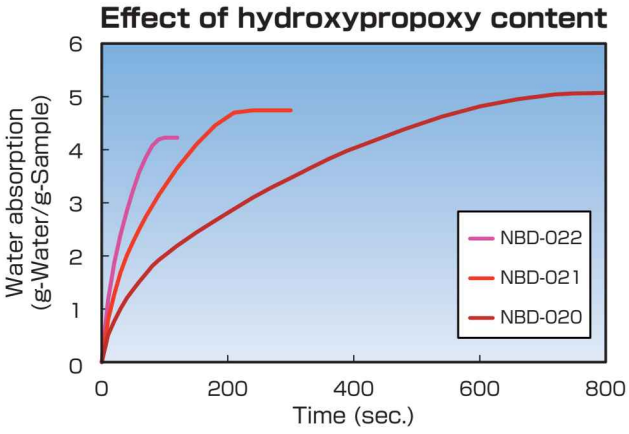
# Water Absorption

This data shows water absorption through a bed of 1 g disintegrant powder using an apparatus shown on the right. Similar to the swelling property, the water absorption level depends on particle size and hydroxypropoxy content. Compared to the other super disintegrants, L-HPC absorbs a larger amount of water and reaches a plateau in a shorter time.



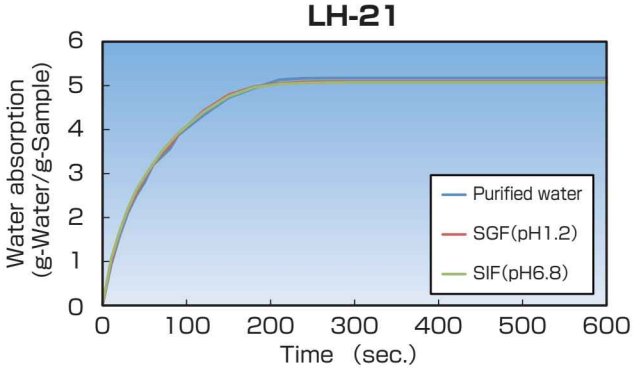



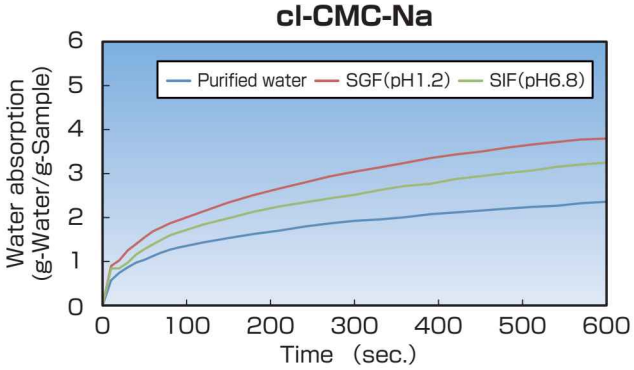




## ◆ Effect of test fluid

Water absorption was tested using various test fluids. L-HPC shows pH-independent characteristics. In contrast, the behavior of ionic disintegrants was depended on test fluids.

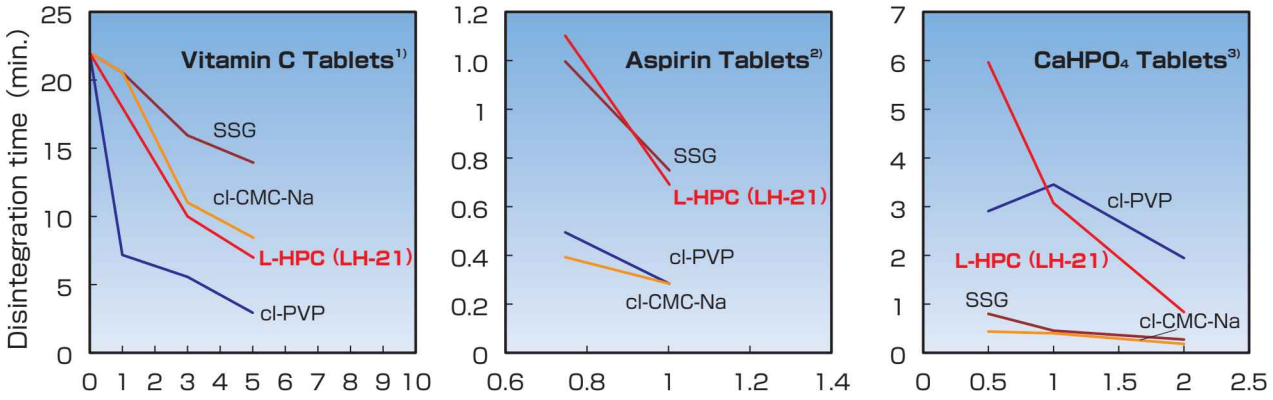


# Disintegration and Compressibility

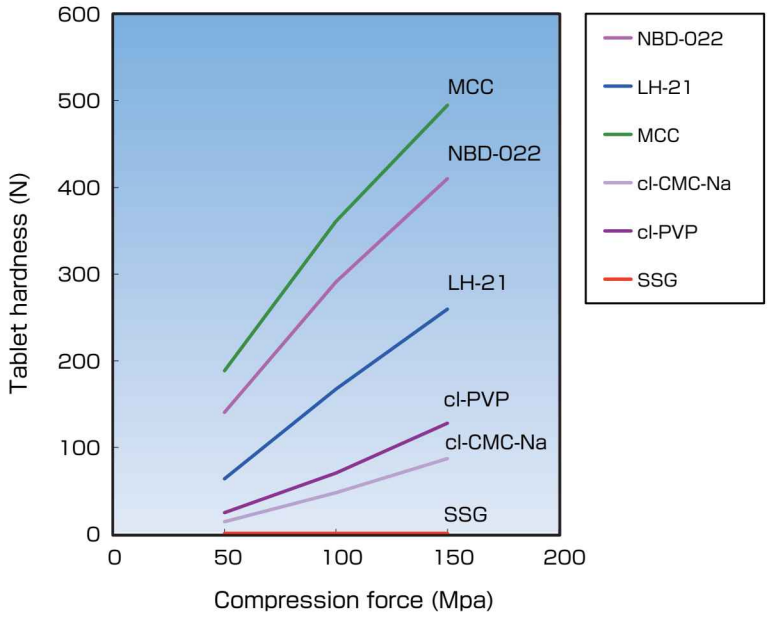
Comparing disintegration capability of various disintegrants, the capability is dependent on active ingredient and formulation.
Looking at the data shown below, L-HPC has similar disintegration capability to the other "super-disintegrants." L-HPC also has a good compressibility compared to the other disintegrants.

## Disintegration of tablets with various disintegrants




1) VC-97 (granulated vitamin C for direct compression), manufactured by Takeda Pharmaceuticals
2) Tablets without disintegrant did not disintegrate up to 2 hrs.
3) Data from a report by Gissinger and Stamm (1980)

## Compressibility of various excipients



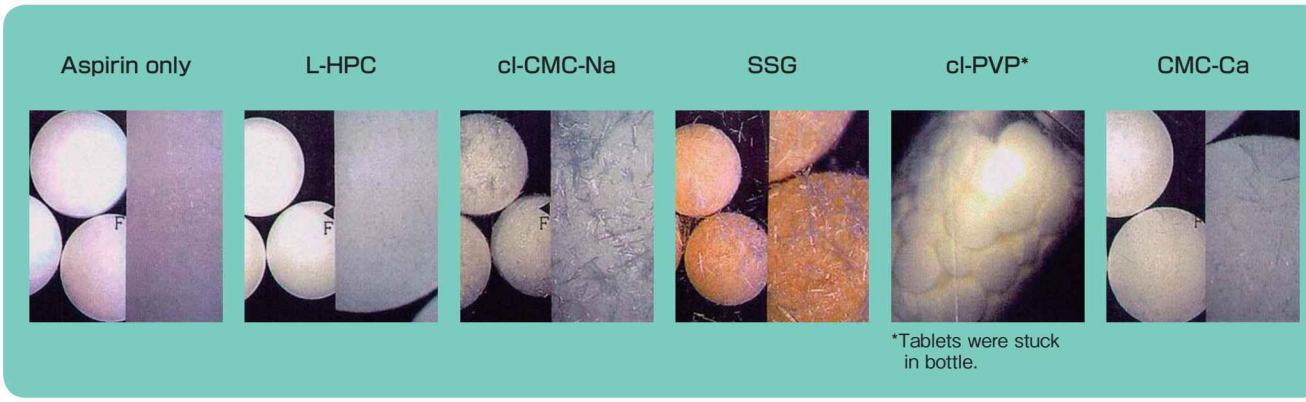

The data is placebo formulation with the size of 480 mg/tab, 12 mm diameter. Tablets were prepared with single punch tablet press (Sankyo Piotech, Japan)

cl-CMC-Na: Croscarmellose sodium
cl-PVP: Crospovidone
SSG: Sodium starch glycolate
MCC : Microcrystalline cellulose PH-101

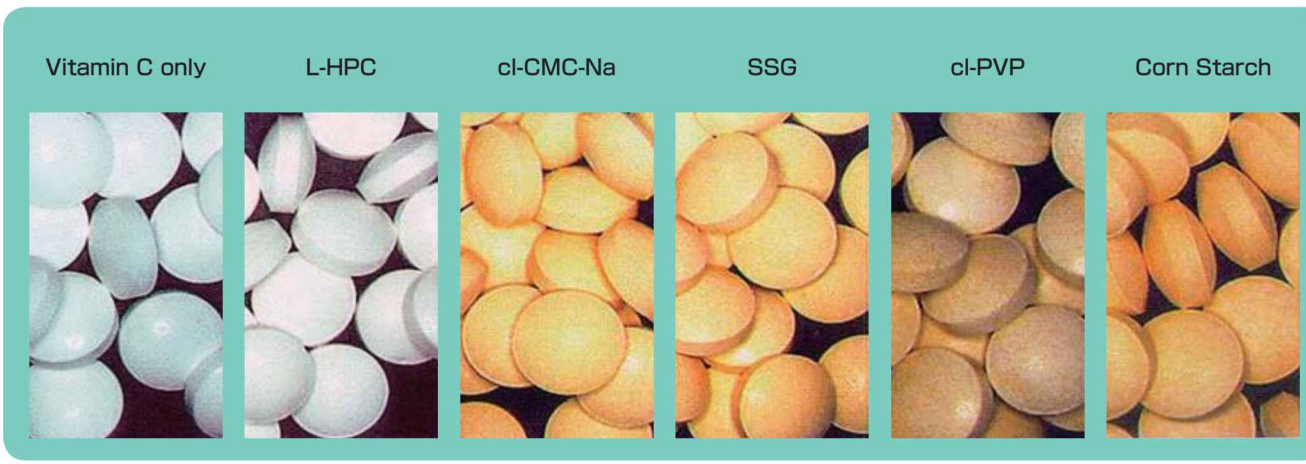
# Compatibility with Active Ingredients

Because L-HPC is non-ionic, it is less reactive to active ingredients compared with ionic excipients. This excellent compatibility is the main reason for L-HPC being the first choice of Japanese pharmaceutical companies.
For example, aspirin tablets with L-HPC were stable under high temperature whereas ionic ingredients showed whiskers of salicylic acid formed by hydrolysis (See picture below).
Vitamin C tablets formulated with L-HPC showed no interaction compared with tablets containing ionic disintegrants. The color stability was even better than with microcrystalline cellulose which is another non-ionic ingredient under the same moisture level. Our further study suggests that this was due to the low water activity of L-HPC because water molecules are bound to the amorphous region of the polymer. All tablets were made by direct compression.

**Aspirin Tablets** – Excipient content: 20%. Stored at 50° C in closed bottle for 3 months.




**Vitamin C Tablets** – Excipient content: 20%. Stored at 50° C in closed bottle for 2 months.

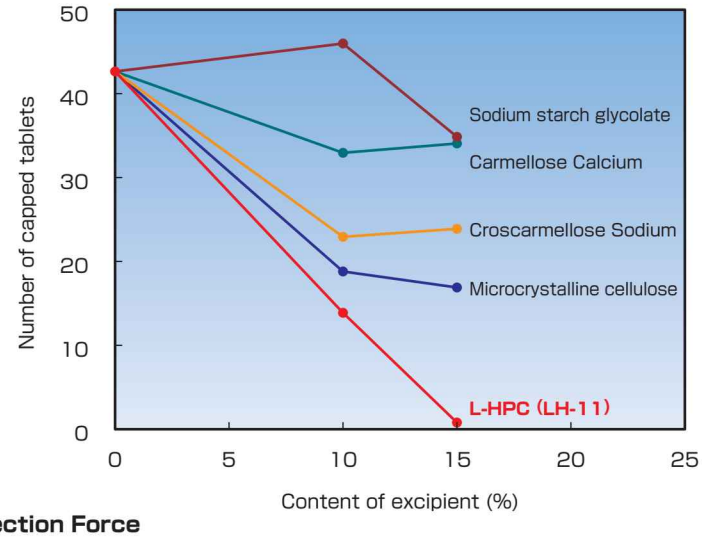


# Anti-capping

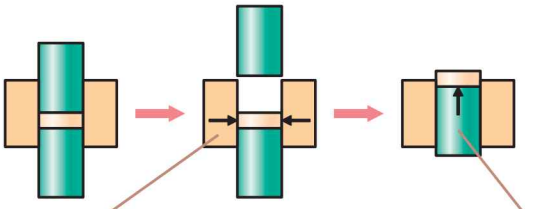
One of the benefits of L-HPC is to resolve "capping," which is a typical problem in the tableting process. Several reports have pointed out that capping is caused by a high residual die-wall pressure during the tableting process. L-HPC reduces the residual die-wall force and ejection force during the tableting process.
LH-11, the highly fibrous grade, is the most effective for anti-capping, as entangling of fibers is important for capping prevention.

## Anti-capping effect of L-HPC
(Ethenzamide tablets)

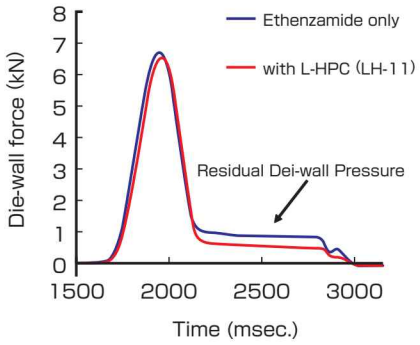
Tablets were prepared by direct compression. Excipients were added from 0 to 15 % in tablet. 50 tablets were tested using a USP friabilator. They were rotated 750 times, and number of capped tablets was counted.



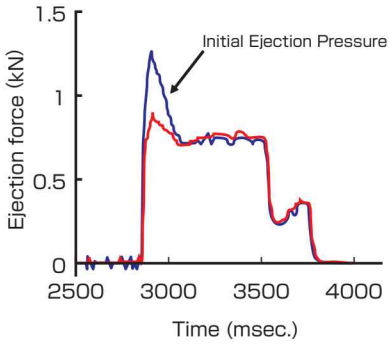

## ◆ Tableting process analysis



### Residual Die-wall Force

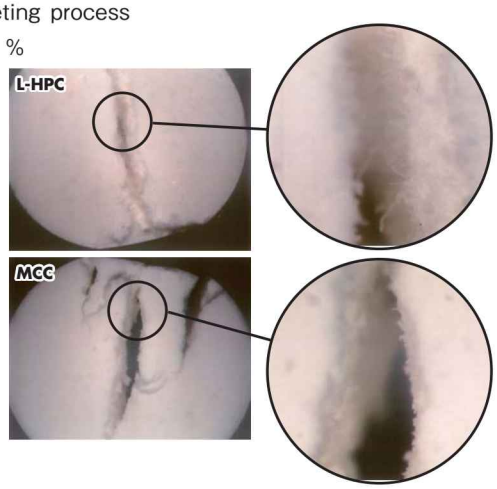



### Ejection Force



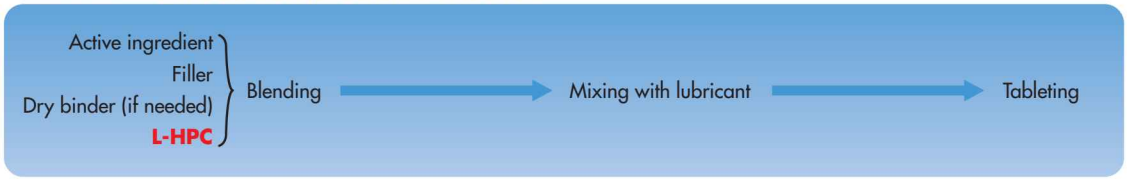

Residual die-wall force and ejection force were measured using a tableting process analyzer (TabAll® Model N30-EX, Okada Seiko, Japan). L-HPC content: 20 %

The above results indicate entangling of L-HPC fibers contributes to better compressibility.
Compared with microcrystalline cellulose (MCC), fibrous structure can be seen in the cracking point of the L-HPC tablet (See the pictures on the right).
Such structure enables tablets to resist against damaging forces from all directions.

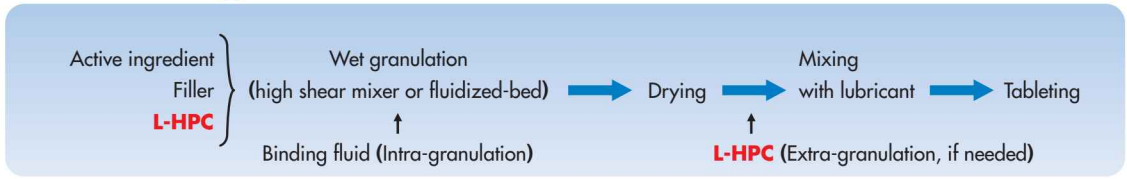


# Applications

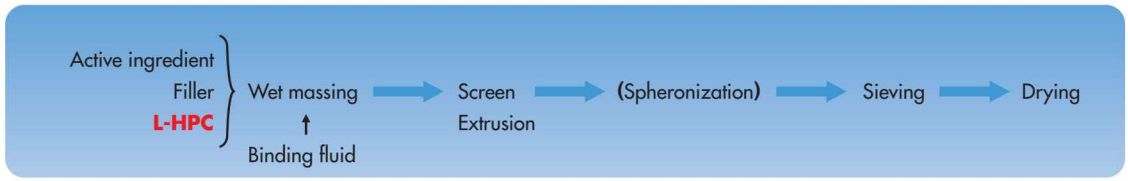
### Tablets – Direct compression method



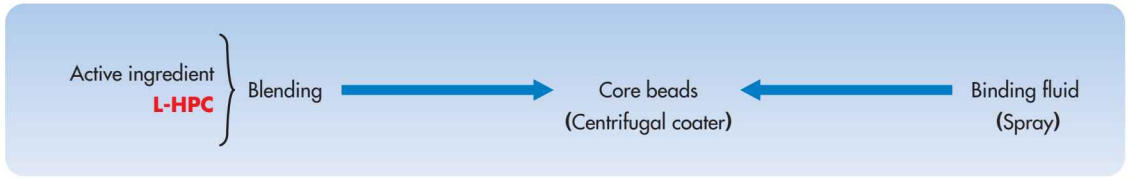

### Tablets – Wet granulation method




### Pellet extrusion




### Drug layering




## ◆ Applications of L-HPC

L-HPC has 9 variations in physical and chemical properties.
Generally, LH grades which have better swelling properties are recommendable for wet granulation methods and NBD grades which have better flowability are more recommendable for direct compression or extra granulation. The standard grades are LH-21 and NBD-021 respectively. Please select the suitable grade in accordance with the below table.

◎ Recommendable ○ Suitable

| Grades | Tablet | | | | | | Pellet | | Others |
|---|---|---|---|---|---|---|---|---|---|
| | Wet granulation | | Direct compression | Anti capping | Dry granulation | ODT | Pellet extrusion | Drug layering | Capsule filling |
| | Intra granulation | Extra granulation | | | | | | | |
| LH-11 | ◎ | ○ | | ◎ | ○ | | | | |
| LH-21 | ◎ | ○ | ○ | ○ | ○ | | | | ○ |
| LH-22 | ○ | ◎ | ○ | ○ | ○ | | | | ○ |
| LH-B1 | ◎ | ○ | ○ | | | | | | ◎ |
| LH-31 | ○ | | | | ◎ | ○ | ◎ | ◎ | |
| LH-32 | ○ | | | | ◎ | ○ | ◎ | ◎ | |
| NBD-020 | ◎ | ○ | ◎ | ○ | ◎ | ○ | ◎ | ◎ | ○ |
| NBD-021 | ◎ | ◎ | ◎ | ○ | ◎ | ◎ | ○ | ○ | ○ |
| NBD-022 | ○ | ◎ | ◎ | ○ | ◎ | ◎ | ○ | ○ | |

# Direct compression

For direct compression, LH-21 and NBD-021 are the primary grade to test. If you especially have a problem of capping, consider using of LH-11 (See page 11). If you need to use a large amount of L-HPC (more than 25 %), consider using LH-B1 (high density grade) for better flowability.

## Direct compression using L-HPC

Formulation:

| | Without L-HPC | With L-HPC |
|---|---|---|
| Ginkgo extract | 20 | 20 parts |
| Spray dried lactose | 80 | 75 |
| L-HPC (LH-21) | - | 5 |
| Mg stearate | 0.5 | 0.5 |

Results:

| | Without L-HPC | With L-HPC |
|---|---|---|
| Tablet hardness (N) | 71 | 76 |
| Disintegration time (min.) | 35.5 | 8.6 |

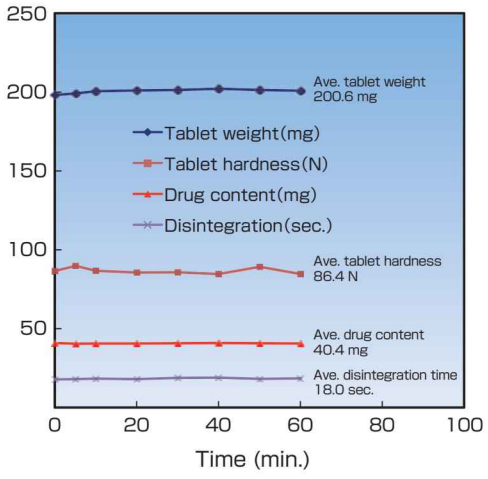
Tableting:
Laboratory scale rotary tableting machine (Virgo®, Kikusui, Japan), Tablet size; 8 mm-d, 6.5 mm-r, 200 mg per tablet, Compression force; Pre 3 kN, Main 10 kN

## High speed tableting using NBD (ODT formulation)

NBD grades are suitable for direct compression as they have narrower particle size distribution and better flowability. They enable to make less variation on tablet weight and drug content.

Formulation

| | |
|---|---|
| Acetaminophen | 20 % |
| Granulated D-Mannitol (Granutol® S) | 69.5 % |
| L-HPC (NBD-022) | 10 % |
| Mg stearate | 0.5 % |




Compression
All components were well blended and compressed into 8 mm diameter and 200 mg weight tablet.
Compression force Pre; 3 kN Main; 10 kN
Rotation speed; 40 rpm
10 tablets were taken at every 5-10 minutes and weight, tablet hardness, disintegration test in water and drug content were analyzed using UV system.

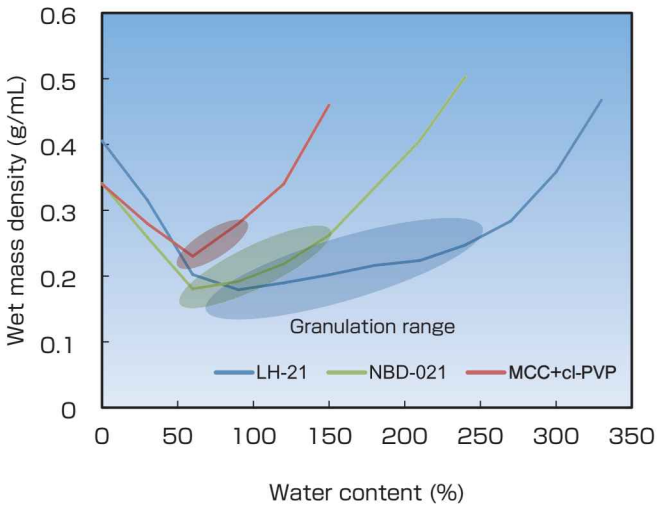
More technical information is available. Please consult us or your local contact.

# Wet granulation (high shear mixer granulation)

In wet granulation, L-HPC gives a "buffer effect" stabilizing the wet-massing process for a wide range of water content. LH-21 is typically used for this purpose. Especially for active ingredients with poor solubility and low wettability, you can use a higher amount of L-HPC to improve disintegration. Even as much as 20 – 40 % of L-HPC has been used in a tablet for this purpose. In spite of such a high content, stability problems are not significant as seen in other ionic disintegrants. In such applications, tablets disintegrate in very fine individual particles, so the dissolution is rapidly completed.

## "Buffer effect" of L-HPC in wet-massing

(Pure material in high shear mixer)

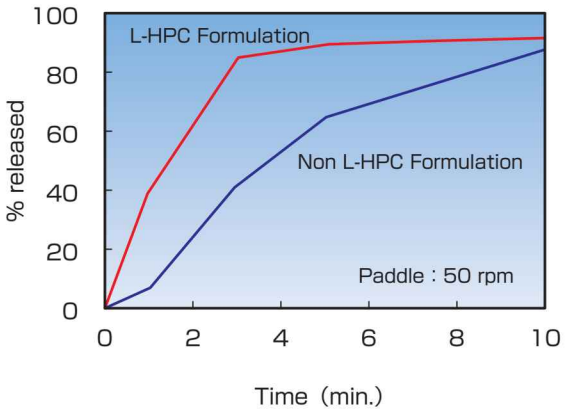



## Disintegration behavior and dissolution of tablets

Process: Wet massing → Sieving → Drying → Tableting

| L-HPC Formulation | |
|---|---|
| Aspirin | 30% |
| Lactose | 45 |
| L-HPC (LH-21) | 25 |

| Non L-HPC Formulation | |
|---|---|
| Aspirin | 30% |
| Lactose | 45 |
| Microcrystalline cellulose | 20 |
| Croscarmellose Sodium | 5 |




More technical information is available. Please consult us or your local contact.

# Wet granulation (fluidized bed granulation)

L-HPC has dual functions, which is a disintegrant and a binder. Therefore it is recommendable excipients not only for high shear mixer granulation but also for fluidized bed granulation. Even with the low compressible drugs, tablets can be prepared as high tablet hardness and quick disintegration by fluidized bed granulation with L-HPC.

Formulation

| | |
|---|---|
| Acetaminophen (fine powder) | 40 parts |
| Lactose (Pharmatose®200M) | 55 |
| Disintegrant (see below table) | 5 |
| Binder solution | 40 |
| (5% aqueous solution of Pharmacoat®603) | |

Processing parameters for granulation

Equipment : Multiplex MP-01 (Powrex corp.)
Spray position : top spray
Charged quantity : 400 g
Inlet temp. : 60 °C
Outlet temp. : 25-27 °C
Airflow : 0.6 $m^3$/min.
Spray air pressure : 150 kPa
Spray air quantity : 35 L/min.
Spray feed rate : 10 g/min.
Drying process : untill the outlet temp. of 45 °C

Processing parameters for compression

Equipment : Virgo®, rotally tableting press (Kikusui Seisakusho Ltd.)
Tablet weight : 200 mg
Tablet size : 8 mm-d, 12 mm-r
Compression force : pre 3 kN, main 7.5 kN
Rotation speed : 40 rpm

## Result

| Disintegrant | Granules properties | | Tablet properties | |
|---|---|---|---|---|
| | Bulk density (g/mL) | Carr's index*1 (%) | Tablet hardness (N) | Disintegration time (sec.) |
| L-HPC NBD-020 | 0.322 | 26.7 | 87.8 | 61.3 |
| L-HPC LH-21 | 0.344 | 24.6 | 70.9 | 61.8 |
| Cl-CMC-Na | 0.370 | 25.3 | 68.9 | 70.4 |

*1 (1-bulk density/tapped density) ×100

More technical information is available. Please consult us or your local contact.

# Pellet Extrusion

As well as tableting, L-HPC is also applicable for pellet extrusion. Micronized grades (typically LH-31) are best suited for this application because smaller particles can easily pass through the screen. L-HPC provides wet mass with a "buffer effect" in which the wet mass accepts a wider range of water content. L-HPC plasticizes wet mass and shows greater productivity (extrusion speed and yield). The final pellets show quick disintegration and better friability compared with non-L-HPC formulations.

**L-HPC formulation:**

| | |
|---|---|
| Aspirin | 93 % |
| L-HPC (LH-31) | 5 |
| Hypromellose (Pharmacoat® 603) | 2 |

**Non L-HPC formulation:**

| | |
|---|---|
| Aspirin | 93 % |
| Microcrystalline cellulose | 4 |
| Croscarmellose Sodium | 1 |
| Hypromellose (Pharmacoat® 603) | 2 |

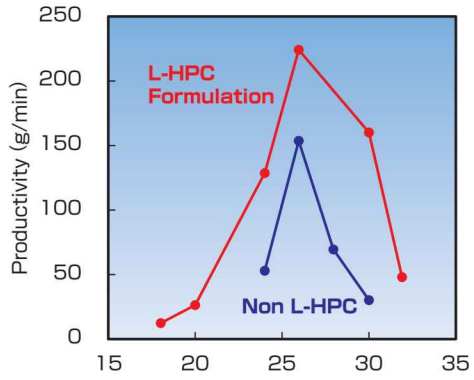
**Process:**

Wet-massing → Extrusion (DomeGran®, Dalton, Japan, 1-mm screen) → Spheronization → Drying → Sieving (0.85 - 1.7 mm)

**Friability test:** USP

**Disintegration test:** USP

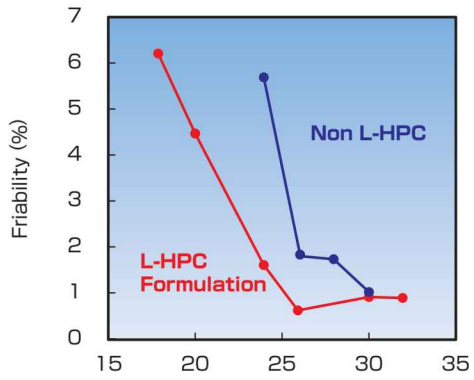
**Productivity* vs. Wet-mass Water**




Water in wet mass (%)

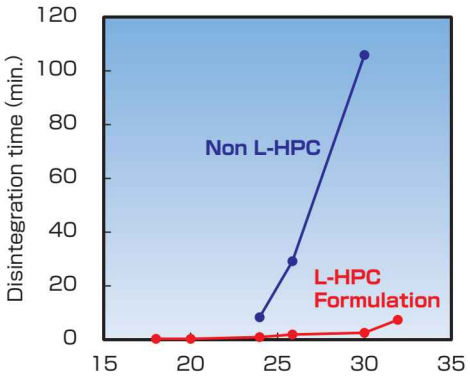
(Productivity* = Extrusion speed × Product yield)

**Friability of Final Pellets vs. Wet-mass Water**




Water in wet mass (%)

**Disintegration of Final Pellets vs. Wet-mass Water**




Water in wet mass (%)

More technical information is available. Please consult us or your local contact.

# Product information

| Grades | Hydroxypropoxy content (%) | Mean particle size* (um) | 90% cumulative particle size * (um) | Tapped density | Particle size ratio ($D_{90}/D_{50}$) |
|---|---|---|---|---|---|
| LH-11 | 10.0 - 12.9 | 45 - 65 | 150 - 200 | - | - |
| LH-21 | | 35 - 55 | 100 - 150 | | |
| LH-22 | 7.0 - 9.9 | | | | |
| LH-B1 | 10.0 - 12.9 | 45 - 65 | 100 - 150 | Not less than 0.65 g/mL | |
| LH-31 | | 17 - 23 | 40 - 100 | - | |
| LH-32 | 7.0 - 9.9 | | | | |
| NBD-020 | 13.0 - 15.9 | 35 - 55 | 70 - 130 | | 1.5 - 3.0 |
| NBD-021 | 10.0 - 12.9 | | | | |
| NBD-022 | 7.0 - 9.9 | | | | |

* Shin-Etsu Laser diffraction method

## Package

50 kg - Fiber drum with polyethylene double bag inside
1 kg - Polyethylene double bag

# Precautions for Safe Handling

## Warning: May form flammable or Explosive dust-air mixtures.

When handling, avoid accumulation and suspension of dust in the air.
Store away from heat sources, sparks, and flame. Do not permit grinding, welding, or smoking near this material.
General precautions outlined in the National Fire Protection Association's NFPA654 "Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustible Particulate Solids" and NFPA 77 "Recommended Practice on Static Electricity" are recommended.

Dust explosivity parameters of L-HPC (LH-32)

| | |
|---|---|
| ● Kst [1)] | 193 bar·m/s |
| ● ST classification [1)] | ST-1 |
| ● Maximum explosion pressure [1)] | 8.4 bar |
| ● Maximum rate of pressure rise [1)] | 710 bar/s |
| ● Minimum explosive concentration [1)] | 60-70 g/m$^3$ |
| ● Minimum ignition energy [1)] | 10-25 mJ |

1) In house data was determined by Chilworth Technology Inc., New Jersey, U.S.A.

## CAUTION: May cause eye irritation.

Avoid contact with eyes, skin and clothing.
Wash thoroughly after handling.
Wash contaminated clothing before re-use.
Use only with adequate exhaust ventilation.
Follow an organized housekeeping plan.
Keep floors and equipment clean.

## Emergency and first aid procedures

If inhaled: Remove to fresh air. Give artificial respiration if breathing stops. Get immediate medical attention.
In case of eye contact: Flush eyes with plenty of fresh water while holding eyelids open. Get immediate medical attention.
In case of skin contact: Wash off with flowing water.

## In case of material spills and leakages

The following steps should be taken.
- Wear an approved respirator, rubber gloves, rubber boots and safety goggles.
- Vacuum or sweep up spillage. Prevent dust generation. Place spillage in an appropriate container for waste disposal.
- Ventilate area and wash spill site.
- Wash contaminated clothing before reuse.

## Storage

Keep dry. Store away from excess heat and sunlight. Store in sealed containers.

## Disposal

Contents: Dispose of unused contents in accordance with all applicable federal, state and local laws.
Consult the distributor for further information.
Container: Do not re-use container. Dispose of empty container by the procedures approved by federal, state and local authorities.

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Carefully read and understand the material Safety data sheet (SDS) before using this product.

**N O T E :**

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