The Specialty Excipient

Neusilin®

A totally synthetic magnesium aluminometasilicate (MAS) with exceptional excipient properties to improve API delivery and the quality of pharmaceutical preparations

Fuji Chemical Industries
Table of Contents

Characteristics ....................................................................................... 4
Chemical formula .................................................................................. 4
General properties ................................................................................ 5
Neusilin® grades ................................................................................... 5
Typical properties ................................................................................ 6
Typical applications and quantity needed in pharmaceutical preparations ................................................................................................................... 6
Pharmaceutical applications ................................................................................
  I. Oil and extracts to powder .................................................................... 7
  II. Flowability Improvement ..................................................................... 7
  III. Anti caking ....................................................................................... 7
  IV. Compressibility ................................................................................. 8
  V. Solid dispersion .................................................................................. 8
  VI. Hygroscopic velocity curve ................................................................. 8
  VII. Hygroscopic equilibrium curve ......................................................... 8
  VIII. Most compatible disintegrants ......................................................... 8
Cosmetic applications ............................................................................. 9
Package size ........................................................................................... 10
Pharmacopoeia and regulatory information ............................................ 10
Dosage and safety ................................................................................... 11
Stability .................................................................................................. 12
Conclusions ........................................................................................... 13
Further reading ....................................................................................... 15
Neusilin® - The specialty excipient

Neusilin® is a synthetic, amorphous form of magnesium aluminometasilicate. It is a multifunctional excipient that can be used in both direct compression and wet granulation of solid dosage forms. Neusilin® is widely used for improvement of the quality of tablets, powder, granules and capsules.

Neusilin® does not develop gel with aqueous solutions unlike other magnesium aluminum silicates. The different grades of Neusilin® have been highly evaluated at home and abroad. It has a market presence of over 60 years in Japan.

**Chemical formula**

\[ \text{Al}_2\text{O}_3 \cdot \text{MgO} \cdot 1.7\text{SiO}_2 \cdot x\text{H}_2\text{O} \]

Neusilin® is amorphous and contains either tetrahedron or octahedron of Al, octahedron of Mg and tetrahedron of Si which are randomly attached to form a complex three dimensional structure. Neusilin® does not possess repeating units of a defined monomer.

**Characteristics**

1. Neusilin® is Magnesium Aluminometasilicate in either fine powder or granule form.
2. Neusilin® is represented by an empirical formula \( \text{Al}_2\text{O}_3 \cdot \text{MgO} \cdot 1.7\text{SiO}_2 \cdot x\text{H}_2\text{O} \).
3. Neusilin® is amorphous, possesses very large specific surface area and has high oil and water adsorption capacity.
4. Neusilin® is superior in compressibility which enables to make hard tablets at low compression force. It can also improve hardness of other fillers and binders of low concentration.
5. Compounding with Neusilin® helps stabilize moisture sensitive as well as lipophilic APIs.
6. Neusilin® is stable against heat and has a long shelf life.
7. Neusilin® is available in various grades. The grades differ in their bulk density, water content, particle size and pH.
8. Neusilin® is an excellent carrier for solid dispersion via self-micro emulsifying drug delivery system (SMEDDS) and Hot-Melt Extrusion.
General properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White powder or granules</td>
</tr>
<tr>
<td>Physical form</td>
<td>Amorphous</td>
</tr>
<tr>
<td>True specific gravity</td>
<td>2.0-2.2</td>
</tr>
<tr>
<td>Solubility</td>
<td>Practically insoluble in water and ethanol</td>
</tr>
<tr>
<td>Composition (%) on dried basis</td>
<td>Al₂O₃ – 29.1 – 35.5</td>
</tr>
<tr>
<td></td>
<td>MgO – 11.4 – 14.0</td>
</tr>
<tr>
<td></td>
<td>SiO₂ – 29.2 – 35.6</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>Less than 20 to 5% depending on grades</td>
</tr>
<tr>
<td>CAS Number</td>
<td>12511-31-8</td>
</tr>
<tr>
<td>EINECS number</td>
<td>235-682-0</td>
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</table>

Neusilin® grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>UFL2</th>
<th>US2</th>
<th>S1</th>
<th>S2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Alkaline</td>
<td>Alkaline</td>
</tr>
<tr>
<td>Powder</td>
<td>Granule</td>
<td>Granule</td>
<td>Granule</td>
<td>Granule</td>
</tr>
<tr>
<td>Low water</td>
<td>Low water</td>
<td>High water</td>
<td>Low water</td>
<td></td>
</tr>
</tbody>
</table>

Electron micrographs

UFL2

US2

S1

S2
Typical properties

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Alkaline</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>Appearance</td>
<td>White granule</td>
<td>White granule</td>
</tr>
<tr>
<td>Degree of whiteness (%)</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Loss on drying (%) 110°C, 7 hours</td>
<td>13 - 20</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Bulk density Loose (g/ml)</td>
<td>0.30 - 0.37</td>
<td>0.29 - 0.37</td>
</tr>
<tr>
<td>Tapped (g/ml)</td>
<td>0.36 - 0.43</td>
<td>0.34 - 0.42</td>
</tr>
<tr>
<td>True specific gravity</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Specific surface area (m²/g)*1</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>Average particle size (μm)</td>
<td>112</td>
<td>115</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Oil adsorbing capacity (ml/g)*2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Water adsorbing capacity (ml/g)</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Acid consuming capacity (ml/g)*3</td>
<td>≥210</td>
<td>≥210</td>
</tr>
<tr>
<td>pH (4% slurry)*4</td>
<td>8.5 - 10.0</td>
<td>8.5 - 10.0</td>
</tr>
</tbody>
</table>

*1) BET surface area, nitrogen adsorption method
*2) Japanese Industrial Standard pigment test method (JIS K5101)
*3) Amount of 0.1 N hydrochloric acid neutralized by 1 g dried product (110°C, 7 hours)
*4) Weigh 2 g of sample, add water to make 50 ml. After stirring, allow to stand for 2 minutes, Measure pH using pH meter

Typical applications and quantity needed in pharmaceutical preparations

<table>
<thead>
<tr>
<th>APPLICATION / FUNCTION</th>
<th>Quantity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
</tr>
<tr>
<td>Diluent in solid dosage forms</td>
<td>30-90</td>
</tr>
<tr>
<td>Binder, increasing hardness, disintegration aid in tablets</td>
<td>5-20</td>
</tr>
<tr>
<td>Increase flowability</td>
<td>-</td>
</tr>
<tr>
<td>Anti-caking agent</td>
<td>-</td>
</tr>
<tr>
<td>Solidification of liquid API (eg: oil to powder)</td>
<td>-</td>
</tr>
<tr>
<td>For suspensions</td>
<td>-</td>
</tr>
<tr>
<td>Stabilization of deliquescent drugs</td>
<td>-</td>
</tr>
<tr>
<td>Solid dispersion, SMEDDS</td>
<td>-</td>
</tr>
</tbody>
</table>
Pharmaceutical applications

I. Oils and extracts to powder

Schematic flow

![Schematic flow diagram]

Oil adsorption capacity

![Oil adsorption capacity chart]

Neusilin® US2 and UFL2 grades show higher oil adsorption capacity* when compared to MCC or colloidal silica.

*Linseed oil direct adsorption

Free flowing powder of linseed oil

![Free flowing powder of linseed oil]

**Neusilin® US2** +30% linseed oil, Dry at 50°C

Linseed oil tablet, Ø11.3mm, 125N at 500 kg/cm²
A mixture containing 25% Scopolia extract or soybean oil and 25% UFL2 was compounded with equal amount of lactose. This mixture was subjected to static compression and tabletting. We found no adhesion to pestle and mortar and the compressibility was good. The tablet did not exude the extract or oil during storage.

An ethanol solution of tocopherol acetate (VE) 20-50% was compounded with proportional amount of Neusilin® and mixed well. To this mixture, 3% croscarmellose sodium and 1% magnesium stearate were added before tabletting. High quality tablets with a load of up to 30% vitamin E can be prepared with Neusilin® US2.
II. Flowability Improvement

Angle of repose after adding Neusilin® and other excipients to potato starch

![Graph showing angle of repose and concentration for different excipients](image)

Neusilin® particles stick to the surface and aid flow

**Potato starch only**

![Electron micrograph of potato starch only](image)

**(x 1,000)**

**(x 10,000)**

**Potato starch + Neusilin® UFL2**

![Electron micrograph of potato starch with Neusilin® UFL2](image)

**(x 1,000)**

**(x 10,000)**

Electron micrograph showing Neusilin® UFL2 particles sticking to the starch surface. On addition to starch, the UFL2 particles stick to the surface and facilitate flow as in a ‘roller blade’ model. A 0.5% addition of UFL2 to potato starch vastly improves flowability.
III. Anti caking

Addition of 0.5% Neusilin® prevents caking

Neusilin® prevents caking at high humidity conditions

Condition: at 45°C, 75% RH, 2 days
IV. Compressibility

Neusilin® increases hardness of lactose tablet

Compounding lactose with 10% Neusilin® UFL2 results in higher hardness when compared to 15% microcrystalline cellulose

High quality tablets at low compression force

Tablet hardness of cornstarch/lactose based tablets compounded with either using Neusilin® US2, colloidal silica or calcium silicate. Corn starch, lactose and excipient were mixed thoroughly. Magnesium stearate as lubricant was added prior to tabletting. Compression with Neusilin® US2 generally gives harder tablets compared to that with colloidal silica.
V. Solid dispersion

Formulating poorly water soluble drugs by solid dispersion leads to a remarkable improvement in dissolution and bioavailability. Neusilin® can potentially resolve problems associated with tabletting and improve efficiency of solid dispersion.

Key advantages of Neusilin® as an adsorbent

- Flowability improvement
- High quality tablets at low compression forces
- High specific surface area
- High adsorption capacity
- Higher API load
- Restriction on reversion of amorphous form to crystalline state
- Inert core material

Case Study I

Solid dispersion granules


Dissolution profile of solid dispersion granules

Comparison of drug dissolution (after 30 min) from initial and stored solid-dispersion granules using USP Type II apparatus at 50 rpm. Data are shown for drug dissolution (% of initial) from solid-dispersion granules after storage at 40°C/75% RH (Gupta et al, 2002)
Case Study II  US2
Solid SEDDS (self-emulsifying drug delivery systems) formulation
Use of Neusilin® as adsorbent carrier to convert liquid SEDDS to solid SEDDS

1. Glyburide SEDDS tablets

Self micro emulsifying formulation was prepared by adding under continuous stirring Tween 20 and Labrafac Hydro® WL (oil phase) and then distilled water to glyburide solubilized in Transcutol®. Glyburide tablets were prepared by direct compression. The preparation with Neusilin® US2 resulted in improved flow, compact tablets and improved dissolution profile.

Dissolution profile of glyburide preparation

Glyburide (GLY) dissolution profile from the different tablet formulations (Ref. Tablet – commercial GLY formulation; SME tablet – glyburide SME formulation consisting of Labrafac Hydro® as oil phase, Tween 20 as surfactant and Transcutol® as co-surfactant; TC tablet – glyburide formulation consisting of Transcutol® (TC) glyburide.

2. Solid SEDDS of paliperidone

Optimized SEDDS formulation containing oleic acid, Tween 80 and Capmul® MCM L8 was adsorbed onto Neusilin® US2 to produce solid SEDDS (SEDDS-N). To understand the release behavior of paliperidone from solid SEDDS and pure drug, in-vitro dissolution test was performed.

Dissolution profile of paliperidone powder
The drug release was faster and the dissolution efficiency was higher for the solid SEDDS compared to that of crystalline form.
HME of Sulindac-Neusilin® Drug Complex
Blends of Sulindac-Neusilin® in 1:1 and 1:2 (w/w ratio) were prepared by HME at 200°C.

Physical / Chemical Stability of Sulindac-Neusilin® HME Complex
The HME samples remained amorphous after 3 months of storage at 40°C/75% RH. The samples were found to remain amorphous for more than one year at ambient conditions.

Sulindac-Neusilin® HME tablets
Sulindac-Neusilin® 1:2 HME tablets showed 100% release in 90 minutes as against 9% release of Sulindac-Neusilin® crystalline tablets.

Dissolution profiles of HME Sulindac-Neusilin® tablets
VI. Hygroscopic velocity curve

1) 37°C, RH 53%

2) 37°C, RH 75%

3) 37°C, RH 92%
VII. Hygroscopic equilibrium curve

The hygroscopic equilibrium curve of different grades of Neusilin® indicate that Neusilin® absorbs very low amount of moisture up to 70% RH.

VIII. Most compatible disintegrants

The most compatible disintegrant with Neusilin® US2 was found to be croscarmellose sodium (Ac-Di-Sol) followed by cross-linked polyvinylpyrrolidone (Kollidon CL) and carmellose calcium (ECG-505). The characteristics (large surface area and porus nature) of US2 and the cross linking of croscarmellose sodium act synergistically allowing the tablet to swell and absorb many times of its weight in water leading to quick disintegration. Neusilin® US2 improves flowability and makes sufficiently hard tablets at low compression forces. Increase in hardness and compression force did not affect the disintegration time or tablet conformity when croscarmellose sodium was used as a disintegrant.

As most of the starch-type disintegrants do not go well with Neusilin® US2, croscarmellose sodium is your best choice when you choose Neusilin® US2 in your formulations.
Cosmetic application (UFL2)

Unique properties of Neusilin® UFL2 make it an ideal component for cosmetic preparations. Although chemically the same as traditional crystalline Magnesium Aluminum Silicate (MAS), Neusilin® is both structurally and functionally very different. While MAS is used as a thickener, Neusilin® does not develop viscosity or form gel. It is formulated in facial care products including lotions, eye shadow, cleansers, powders, acne and oily skin treatments and deodorants.

**Neusilin® UFL2 applications**

- **Function**
  - Cleaner
  - Mattifier
  - Body care

- **Stabilizer**
  - Base cosmetics
  - Color cosmetics

- **Production**
  - Sodium polyacrylate
  - Gel formulation (face/eye masks)

Oil adsorption

Neusilin® possesses excellent adsorption capacity for its extremely large specific surface area and porous reticulate structure. It can adsorb up to 330% of its own weight and maintains its powdery state. This superior adsorption capacity makes Neusilin® ideal for applications including oily and acne skin treatments.

Deodorization

Neusilin® works to eliminate odor in two ways. It can neutralize odor through making hydrogen bonds with bad odor compounds such as isovaleric acid or through covalent bonding with ammonia and trimethylamine. It can also physically absorb foul odor compounds by trapping them into its highly porous structure.

**Functionalities**
- Excellent sebum absorption capability
- High oil and water absorption
- Deodorant properties
- Pigment dispersion aid
- Anti-caking agent
- Opacifying agent
- Ideal for powder lotions and other personal care products

**Effective oil adsorption**

![Bar chart showing adsorption of oleic acid](chart)

*Oleic acid adsorbed was washed with ethyl ether to determine the efficiency of adsorption.

**Odor adsorption**

<table>
<thead>
<tr>
<th>Foul odor</th>
<th>Concentration / Amount used</th>
<th>Odor eliminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>1,000 ppm / 100 mg</td>
<td>79.5%</td>
</tr>
<tr>
<td></td>
<td>1,000 ppm / 200 mg</td>
<td>96.2%</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>435 ppm / 100 mg</td>
<td>81.6%</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>697 ppm / 100 mg</td>
<td>31.4%</td>
</tr>
<tr>
<td>Isovaleric acid</td>
<td>262 ppm / 20 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>849.8 ppm / 100 mg</td>
<td>99.6%</td>
</tr>
<tr>
<td>Propionic Acid</td>
<td>382.3 ppm / 20 mg</td>
<td>100%</td>
</tr>
<tr>
<td>N-butyric Acid</td>
<td>311.8 ppm / 20 mg</td>
<td>100%</td>
</tr>
</tbody>
</table>
Neusilin® is a stable inorganic compound and meets JPC and NF specifications. The shelf life of Neusilin® is 3 years from the date of manufacture.

Samples are available upon request. Please contact your local distributor or sales representatives.

Pharmacopoeia and regulatory information
Neusilin® meets all the requirements of the current USP/NF and JPC. An US DMF type IV filed in 1998.

Dosage and safety
Neusilin® is safe with no reports of adverse reactions and is an accepted ingredient by the USP/NF and JPC. Based on the usage as an excipient in various formulations in Japan, Neusilin® up to 1.05 g can be used for oral uptake per day.* There are no established maximum oral intake limits specified by US-FDA.

*Encyclopedia of Pharmaceutical Additives, Japan, 2005

Stability
Neusilin® is a stable inorganic compound and meets JPC and NF specifications. The shelf life of Neusilin® is 3 years from the date of manufacture.

Conclusions
Neusilin® is a totally synthetic magnesium aluminometasilicate with exceptional excipient properties to improve API delivery and quality of oral solid-dosage form pharmaceuticals. Neusilin® is available in four grades and the two different pH options make it a versatile excipient for a wide-variety of applications.

With over 500 pharmaceutical preparations and a market presence of over 60 years in Japan, Neusilin® is well accepted by the formulators world-wide as an aid for formulations containing antibiotics, oily actives, poorly water soluble APIs, herbal mixtures, vitamins, etc. Neusilin® is also used as carrier for preparation of solid dispersion and self-micro emulsifying drug development systems.

Neusilin® has been demonstrated as an excellent adsorbent carrier for solid dispersion preparation via hot melt granulation, Self Micro-Emulsifying Drug Delivery Systems (SMEDDS) for BCS class II drugs such as meloxicam, naproxen, ketoprofen, glyburide and other highly permeable but poorly water soluble drugs. The most exciting use of Neusilin® is in Hot Melt Extrusion (HME). Neusilin® allows preparation of stable amorphous drug complex without any addition of polymers, waxes or plasticizers normally associated with HME. The samples can be recovered as amorphous powder and converted to highly stable tablets through direct compression.
Further reading

Neusilin®