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Pharmaceutical Excipients

FREUND CORPORATION

INDEX

Pioneering the future in creativity

Institute for Technology Development

Freund's functional excipients which meet a variety of needs

Freund succeeded in developing the automatic film coating equipment and film coating excipient for the first time in the world after its inception in April 1964 and started these businesses.

Freund's technology laboratory institute with the experts of pharmaceutical, food, applied chemical, chemical engineering, biochemistry, electronic engineering, mechanical engineering, has conducted innovative product development, has launched many unique products and gained high evaluation from various field.

The functional excipients division has countless experience and successful performance especially in pharmaceutical industry. It actively pursues development of new material and technology.

High quality excipients for better pharmaceutical drugs

Recent years see progress of studies how drugs can be absorbed, distributed and show their effects in human body. Based on these results, drug formulation technologies tailored to the characteristics of the drugs have been pursued.

In line with this, role of pharmaceutical excipients has become further clarified and their importance has increased.

Pharmaceutical excipients do not have their own medicinal effect. Nevertheless pharmaceutical excipients play so much important roles that they affect original purpose of drugs depending on their selection.

Freund is conducting research and development of various excipients in order to meet the current drug formulation needs with the corporate philosophy of "Develop the Future by Creativity".

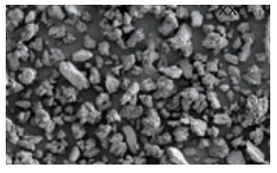
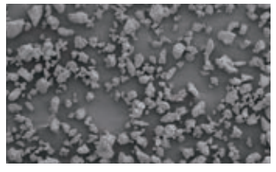
Pharmaceutical Excipients

Dilactose™

Dilactose™ is developed by our unique fluid bed granulation method. It is useful as an excipient for direct compression. Dilactose™F (Fine) is small particle size grade Dilactose™. In comparison with the existing grades, both formability and disintegration have been improved.

Line-up

We have 2 different types with different particle sizes.

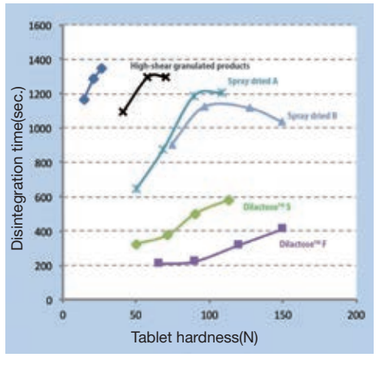
Type			Dilactose™ S	Dilactose™F (Filne)
Compendial			Lactose Hydrate JP Lactose Monohydrate USP-NF, Ph. Eur.	Lactose Hydrate JP Lactose Monohydrate USP-NF, Ph. Eur.
Particle size specification			355 μm on Not more than 2% 355~75 μm 50-70% 75 μm pass 30-50%	180 μm on Not more than 2% 180~53 μm 50-80% 53 μm pass 20-50%
Physical properties	Particle size distribution	D_{10}	51 μm	33 μm
		D_{50}	94 μm	64 μm
		D_{90}	169 μm	124 μm
	Bulk density		0.55 g/mL	0.47 g/mL
	Angle of repose		38°	39°
SEM images				

* Physical properties are representative values, not specifications.

Features

Well-balanced between compression formability and disintegration

Lactose manufactured by high-shear granulation is generally inferior in compressive formulation. On the other hand, lactose manufactured by the spray dry method has excellent compressive formability but conversely tends to be inferior in disintegration. In comparison, Dilactose™, which is manufactured by the fluid bed granulation method, is excellent on both counts so it is possible to obtain tablets with high hardness and fast disintegration.



Excellent Mixability and Fluidity

Even though the particle size of Dilactose™ S is very fine in order to enhance mixability with API, it has excellent fluidity. This comes from the manufacturing process because lactose crystals are all finely granulated.

Excellent Storage Stability

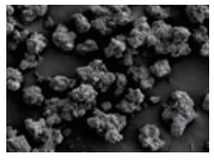
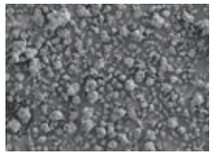
Absorbency is not as high as spray dry lactose so there is extremely low potential for the occurrence of caking over time.

Granutol™

Granutol™ is an excipient for the direct compression of D-Mannitol, using an application of the Dilactose™ (directly compressible lactose) technology cultivated by our company. We have 3 different types with different particle sizes.

Line-up

We have 3 different types with different particle sizes.

Type			Granutol™ R	Granutol™ S	Granutol™ F (Fine)
Compendial			D-Mannitol JP Mannitol USP, Ph. Eur.	D-Mannitol JP Mannitol USP, Ph. Eur.	D-Mannitol JP Mannitol USP, Ph. Eur.
Particle size specification			500 μm on Not more than 2% 500~75 μm Not less than 80% 75 μm pass Not more than 20%	500 μm on Not more than 2% 500~75 μm Not less than 50% 75 μm pass 20~50%	250 μm on Not more than 2% 250~45 μm 40~80% 45 μm pass 20~60%
Physical properties	Particle size distribution	D_{10}	78 μm	41 μm	35 μm
		D_{50}	154 μm	83 μm	65 μm
		D_{90}	253 μm	147 μm	137 μm
	Bulk density		0.53 g/mL	0.55 g/mL	0.49 g/mL
	Angle of repose		34°	33°	39°
SEM images					

* Physical properties are representative values, not specifications.

Features

Excellent compression formability and fluidity

Granutol™ has good compression formability to avoid compression problems such as capping and sticking. It also has excellent fluidity for direct compressive excipient.

Suitable excipient for orally disintegrating and chewable tablets

D-Mannitol is moderately sweet and has cool taste so that it has good dose feeling. Combination with appropriate volume of disintegrating agents provides quickly disintegrating effect to tablets in the mouth.

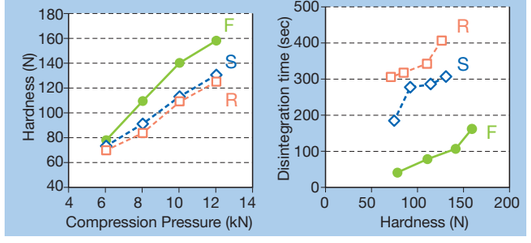
It has a finer particle grade

Granutol™ F, finer grade of Granutol™, has excellent disintegrating effect with the same compression formability in comparison with spray dried mannitol.

Physical Properties of Granutol Tablets

Formulation S, R : Granutol: Mg-St=100:1.0
F : Granutol: Mg-St=100:1.2

Tabletting 8mmϕ -10R, 200 mg/Tab, Speed : 50 rpm



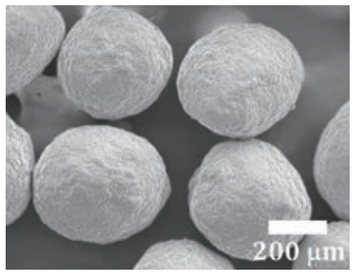
NONPAREIL™

High sphericity makes it possible to calculate volume and surface dimension and it is easy to control film thickness in controlled-release drugs.
Narrow particle size distribution When layering drugs, granules with sharp particle size distribution can be obtained. In addition, the thickness of film does not vary in the layering process and the speed of API release very stable.

Line-up

NONPAREIL™ has 3 different types of composition and it is possible to select a type according to API interaction or usage. There are following grades with different particle sizes.

Type	NONPAREIL™-103	NONPAREIL™-105	NONPAREIL™-108
Ingredients	Purified sucrose	Lactose Microcrystalline cellulose	D-Mannitol
Compendial	Purified Sucrose Spheres JPE (US DMF registered)	Lactose·Microcrystalline Cellulose Spheres JPE (US DMF registered)	D-Mannitol JP Mannitol USP, Ph. Eur. (US DMF registered)
Grade (particle size)	20-24 (850-710 μm) 24-32 (710-500 μm) 32-42 (500-355 μm)	50-83 (300-180 μm) 150 (212-106 μm)	32-42 (500-355 μm) 200 (250-150 μm) 100 (150-75 μm)



NONPAREIL™-103 (32-42)

NONPAREIL™-103

NONPAREIL™-103 is a spherical granule consists of purified sucrose.

Line-up

Grade		20-24	24-32	32-42
Particle size	Microns	850-710	710-500	500-355
	ASTM	20-25	25-35	35-45
Loss on drying		Not more than 0.20%	Not more than 0.20%	Not more than 0.20%
Physical propertie	Bulk density	0.88 g/mL	0.87 g/mL	0.86 g/mL
	Angle of repose	30°	30°	32°
	Friability	0.40%	0.20%	0.04%

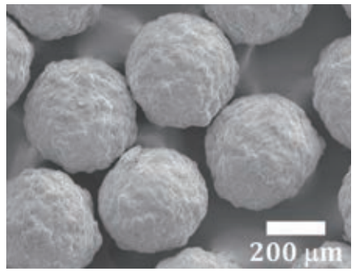
* Physical properties are representative values, not specifications.

Features

100% Purified sucrose
Granule hardness is high and has excellent wear-resistance.
It is completely soluble in water.

Low Free Water (less than 0.1%)
It has very little influence on the stability of API that are interactive with water.

Perfect for Powder Layering
By the high solubility of sucrose in water, layering effectively progresses with a low binder quantity.



NONPAREIL™-105 (50-83)

NONPAREIL™-105

NONPAREIL™-105 is a spherical granule made from lactose and microcrystalline cellulose.

Line-up

Grade		50-83	150
Particle size	Microns	300-180	212-106
	ASTM	50-80	70-140
Loss on drying		Not more than 5.0%	Not more than 5.0%
Physical propertie	Bulk density	0.76 g/mL	0.73 g/mL
	Angle of repose	31°	33°
	Friability	0.29%	0.18%

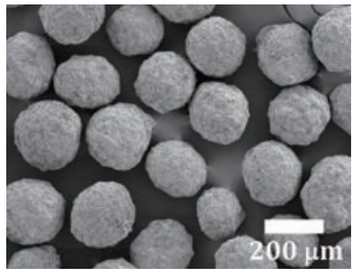
* Physical properties are representative values, not specifications.

Features

High Mechanical Strength
As granule hardness is high and has excellent wear-resistance, there is little damage during granulating/coating process and it makes handling easier.

Sugar Free Composition
Low reactivity with API and low in calories.

Low Cohesiveness
Blocking hardly occurs during storage.



NONPAREIL™-108 (200)

NONPAREIL™-108

NONPAREIL™-108 is a spherical granule made from D-Mannitol.

Line-up

Grade		32-42	200	100
Particle size	Microns	500-355	250-150	150-75
	ASTM	35-45	60-100	100-200
Loss on drying		Not more than 0.5%	Not more than 0.5%	Not more than 0.5%
Physical propertie	Bulk density	0.77 g/mL	0.72 g/mL	0.72 g/mL
	Angle of repose	31°	33°	37°
	Friability	0.28%	0.12%	0.31%

* Physical properties are representative values, not specifications.

Features

D-mannitol 100%
Chemically stable and low interaction with API due to less free water.
It is soluble in water completely.

Small particle size grades are available
100 and 200 grades are effective for capsule miniaturizing, and for ensuring uniformity of minute amounts of API.
Especially 100 grade is most appropriate for core particle for OD tablets.

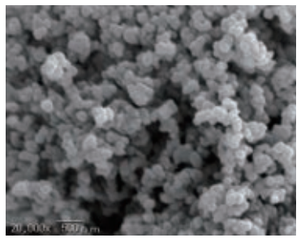
Pharmaceutical Excipients

Titanium Oxide FG

Titanium Dioxide is widely used to protect the colouring of granules, tablets, capsules and API from light. Our high purity titanium oxide has excellent dispersiveness.

Type	Titanium Oxide FG
Compendial	Titanium Oxide JP Titanium Dioxide USP, Ph.Eur.
Mean diameter	Brightness (dispersion liquid of FG 10 g /water 3.5 mL)
0.55 μm	87

* Physical properties are representative values, not specifications.



SEM image

Features

High concealment
Concealing original color by coloring and whitening for tablets and capsules.

Excellent Light-proofing
Protects sensitive API from UV rays and improves stability.

Excellent Dispersiveness in water

Usage Method

This product is usually used by dispersing in water with a homogenizer and adding film or sugar coating liquid.

Adsolider™-101

Adsolider™-101 is a fine powder of silicon dioxide manufactured by the liquid phase method, consisting of high purity silica sand as its raw material.
Compared to products manufactured with the vapor phase method, Adsolider™-101 is rich in porosity with large interior specific surface area.

Type	Adsolider™-101
Compendial	Light Anhydrous Silicic Acid JP Silicon Dioxde USP-NF Colloidal Hydrated Silica Ph.Eur.
Mean diameter (μm)	3.2
Loss on drying (%)	2.6
Volume of oil absorption (mL/100g)	310
pH	7.6
Volume test (mL/5g)	90
Specific surface area (m^2/g)	300

* Physical properties are representative values, not specifications.

Features

Excellent effects in improving fluidity.
In many formulations, adding 0.1 - 0.5% of Adsolider™ improved fluidity. The optimum volume to be added differs depending on the property of mixed powder.

Pill solidity and tablet hardness improves by adding Adsolider™.
With addition of Adsolider™, the hardness of tablet improves by 5-15% without losing disintegration.

Compression pressure	Adding volume	Adsolider™-101	
		Tablet hardness(N)	Disintegration time(sec)
10 kN	0%	54.7	34
	0.4%	58.8	30

* Tablet formulation: Dilactose® S (granulated lactose)/corn starch/microcrystalline cellulose/acetaminophen/Mg-St

Suitable for the powderization of liquids.
Adding 0.5-2 Adsolider™-101 to 1 liquid-type API makes easy powderization.

The pH of Adsolider™-101 is around neutrality (6.0–8.0). It is less interactive with API.

Pharmaceutical Excipients

Lubriwax™-101

It is suitable as a lubricant or a wax matrix former.

Type	Lubriwax™-101		
Compendial	Hydrogenated Oil JP Hydrogenated Caster Oil USP-NF, Ph.Eur.		
Physical propertie	Mean diameter	Bulk density	Melting point
	22 μm	0.36 g/mL	86℃

* Physical properties are representative values, not specifications.

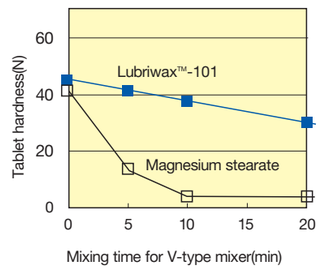
Features

The standard additive volume of Lubriwax™-101 : 0.5 to 5%

Less interaction with API
As it does not contain metal components such as calcium and magnesium or free acids, there are less influences on API stability.

Less influence on tablet hardness
The hardness is less influenced when added to and mixed with tablet powder.

Influence on hardness by mixing time is minimal



Polishing wax™-105

Polishing wax™-105 is a finely powdered Carnauba Wax and it complies with JP, USP-NF, Ph. Eur.
Carnauba wax has the highest melting point among all vegetable-based waxes and it forms glossy layer of shiny membrane so that it is particularly suitable for polishing surface of tablets.

Features

Type	Polishing wax™-105			
Compendial	Carnauba Wax JP USP-NF, Ph.Eur.			
Physical propertie	Mean diameter	Angle of repose	Bulk density	
			loose	tap
	14 μm	45°	0.25 g/mL	0.51 g/mL

* Physical properties are representative values, not specifications.

Polishing wax™ forms glossy surface on sugar coated and filmcoated tablets.

It improves tablets smoothness and handling.

CMEC™

CMEC™ (Carboxymethylethylcellulose) contains cellulose as a raw material and is mixed ether that is obtained by carboxymethylation and ethylation. Listed in JPE and this is mainly used as a base for enteric film coating and controlled-release formulation. In addition, it can be used as a carrier for solid dispersion with the aim of improving the solubility of poorly soluble drugs.

Features

High chemical stability
Consisting of ether linkage, it is chemically stable and hydrolysis hardly occurs.

Agent for enteric and controlled release
The disintegration behavior of tablet coated with CMEC™ depends on pH and independent from buffer solution type. Low pH gives slow disintegration and high pH gives fast disintegration.

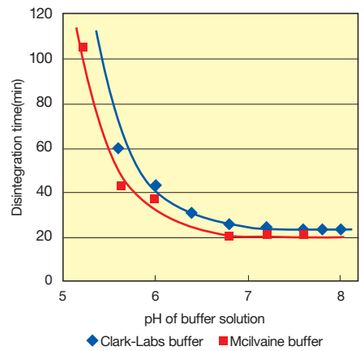
CMEC™ is suitable as an enteric base through controlled-release drugs.

In addition, the combination with controlled release base of pH independency enables forming various dissolution patterns.

Matrix-Forming Material
CMEC™ is also used for a matrix-forming material with API. By changing the ratio of API and CMEC™, it can control releasing speed.

Improve dissolution of poorly soluble drugs
CMEC™ is a carrier of solid dispersion for improving solubility of poorly soluble API.

Protective coating for sugar-coated tablet
CMEC™ is effective as protective coating agent, for tablets containing water-sensitive API by moisture prevention effect with apprx. 100μm thickness.



FREUND Pharmaceutical Excipients Product Table

Trade Name	Grade	Compendial	Components	Appearance	Packing Unit	Conventional Tablet	ODT MUPS	Hard Capsule	Granule	Fine Granule Powder	Main Applications
For Pharmaceutical											
Dilactose™ S		Lactose Hydrate JP Lactose Monohydrate USP-NF, Ph.Eur.	Lactose Hydrate100%	White granulated powder	30kg plastic drum	◎	○	○	◎	○	Directly Compressible Lactose
Dilactose™ F					20kg carton	◎	○	○	◎	○	
Granutol™ R		D-Mannitol JP Mannitol USP, Ph. Eur.	D-Manitol 100%	White granulated powder	20kg carton	○	◎	○	◎		Directly Compressible Mannitol
Granutol™ S						○	◎	○	◎	○	
Granutol™ F						○	◎	○	◎	○	
NONPAREIL™-103	20-24 24-32 32-42	Purified Sucrose Spheres JPE (US DMF registered)	Sucrose100%	White spheres	20kg carton			◎	◎		Spherical core for enteric corting Sustained release granules
NONPAREIL™-105	50-83 150	Lactose・Microcrystalline Cellulose Spheres JPE (US DMF registered)	Lactose Hydrate 60.0～80.0% Microcrystalline Cellulose 40.0～20.0%	White to pale yellowish white spheres	20kg carton	○	◎	◎	○	○	
NONPAREIL™-108	32-42 200 100	D-Mannitol JP Manitol USP, Ph.Eur. (US DMF registered)	D-Manitol 100%	White spheres	20kg carton	○	◎	◎	○	○	
Titanium Oxide FG		Titanium Oxide JP Titanium Dioxide USP, Ph.Eur.	Titanium Dioxide	White powder	25kg carton	◎		○	○		Coloring agent
Adsolider™-101		Light Anhydrous Silicic Acid JP Silicon Dioxide USP-NF Colloidal Hydrated Silica Ph.Eur.	Silicon Dioxide	White to bluish white, light, fine powder	5kg kraft paper bag	◎	◎	○	◎	◎	Absorbent Glidant
Lubriwax™-101		Hydrogenated Oil JP Hydrogenated Castor Oil USP-NF Ph.Eur.	Hydrogenated Castor Oil	White powder	20kg kraft paper bag	◎	○		◎		Lubricant Sustained release base
Polishing wax™-105		Carnauba Wax JP Carnauba Wax USP-NF Ph.Eur.	Carnauba Wax	White to light yellow powder	5kg carton	◎		○			Gloss agent
CMEC™		Carboxymethylethyl cellulose JPE	Carboxymethylethyl cellulose	White to yellowish white powder or granules	10kg carton	◎		○	○		Solid Dispersion Enteric film coating and controlled release agent

◎ most suitable ○ suitable