Pharmaceutical Excipients

Solving Puzzles since 1946

Fuji Chemical Industries Co., Ltd.

Contents

The Specialty Excipient

Neusilin®

$Al_2O_3 \cdot MgO \cdot 1.7SiO_2 \cdot xH_2O$

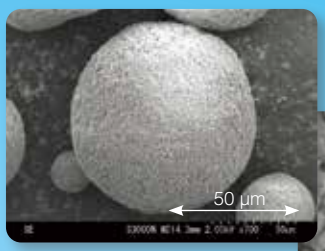
Magnesium aluminometasilicate (JP, USP, EP)

The core benefits of **Neusilin®** as an excipient

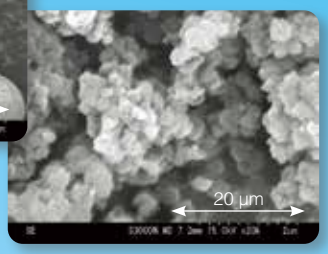
"Multi-problem solver"

Neusilin® solves common problems associated with tableting by facilitating improved and consistent flow of powder mix, providing optimum tablet hardness at low compression forces, protecting the active ingredient from moisture related issues and converting oily or sticky APIs into free flowing powder.

Electron micrograph of **Neusilin®**



A **Neusalin® US2** granule



Internal structure of **Neusalin®**

Neusilin®—The Specialty Excipient

A totally synthetic magnesium aluminometasilicate with exceptional excipient properties to improve API delivery and the quality of pharmaceutical preparations.
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 gels with aqueous solutions unlike other magnesium aluminum silicates do.
The different grades of Neusilin® have been highly evaluated at home and abroad. It has a market presence of over 65 years in Japan.

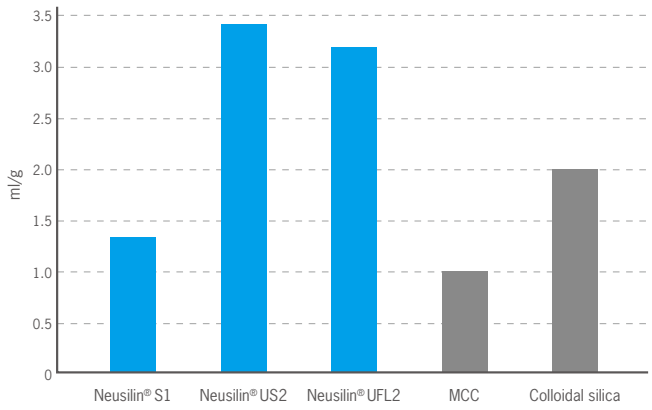
General Properties of **Neusilin®**

Appearance	White powder or granules
Form	Amorphous
True specific gravity	2.0–2.2
Solubility	Practically insoluble in water and ethanol
Compositions (Dried at 110 ˚C) (%)	Al_2O_3 29.1-35.5 MgO 11.4-14.0 SiO_2 29.2-35.6

Neusilin® Features

- Improves tablet and powder capsule quality (US2/UFL2/S1/S2)
- Forms compact tablets with appropriate hardness (US2/S1/S2)
- Oil adsorption of poorly water soluble actives (US2/UFL2)
- Improves powder flowability (UFL2)
- Excellent carrier for solid dispersion (US2)
- Anticaking agent for hygroscopic powders (UFL2)
- Stabilization of deliquescent drugs (UFL2)
- Stabilizer (S1/S2)

Oil Adsorption Capacity



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

* Direct adsorption of linseed oil

Free Flowing Powder of Linseed Oil

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

Linseed oil tablet, Ø11.3mm, 125 N at 500 kg/cm^2

Typical Application and Quantity Required

Grade	S1	S2	US2	UFL2
Tablet binder, disintegrator, increase hardness (%)	5–20	5–20	1–10	1–10
Increase flowability (%)	-	-	-	0.5–5
Stabilization of deliquescent drugs (%)	-	-	5–15	5–15
Excipient/diluent (%)	30–90	30–90	30–90	30–90
Solidification of liquid pharmaceutical preparations (%)	-	-	30–50	30–50
Carrier for solid dispersion, SMEDDS	-	-	20–50	20–50

Application in Solid Dispersions

Neusilin® is an excellent adsorbent carrier for solid dispersion. Solid dispersions can be prepared via hot melt granulation and *hot melt extrusion* (HME) to improve dissolution profile of poorly water soluble drugs. For drugs with high melting points, HME can be prepared simply by mixing of crystalline drug and Neusilin® before passing it through the extruder. The extruded sample can be recovered as amorphous powder and then converted to tablets through direct compression.

Neusilin®'s ability to maintain amorphous state of APIs is well recorded. Several publications and commercial success validate that Neusilin® keeps the drug amorphous and stable under accelerated stability as well as long term storage conditions.

4 Grades to meet a variety of needs

Neusilin® comes in 4 grades that differ in bulk density, water content, particle size and pH. These can be selected according to specific applications.

UFL2	US2	S1	S2
Neutral	Neutral	Alkaline	Alkaline
Powder	Granule	Granule	Granule
Low water	Low water	High water	Low water

Pharmacopoeia & Regulatory

Neusilin® meets all requirements of the current USP/NF, EP and JPC. US DMF Type IV filed.

Further reading

1. Maniruzzaman M, Nair A, Scoutaris N, Bradley MSA, Snowden MJ and Douroumis D. One step continuous extrusion process for the manufacturing of solid dispersions. Int J Pharm. 2015. 496: 42-51
2. Maniruzzaman M, Nair A, Renault M, Nandi U, Scoutaris N, Farnish R, Bradley MSA, Snowden MJ and Douroumis D. Continuous twin-screw granulation for enhancing the dissolution of poorly water soluble drug. Int J Pharm. 2015. 496: 52-62
3. Sohn Y, *et al.*, Development of self-microemulsifying bilayer tablets for pH-independent fast release of candesartan cilexetil. Pharmazie. 2012;67:917-24
4. Kanuganti S, *et al.*, Paliperidone-loaded self-emulsifying drug delivery systems (SEDDS) for improved oral delivery. J Disp Sci Tech. 2012;33:506-15
5. Maclean J, *et al.*, Manufacturing and performance evaluation of a stable amorphous complex of an acidic drug molecule and Neusilin. J Pharm Sci. 2011;100:3332-44

The Unique DCPA

Fujicalin®

$CaHPO_4$

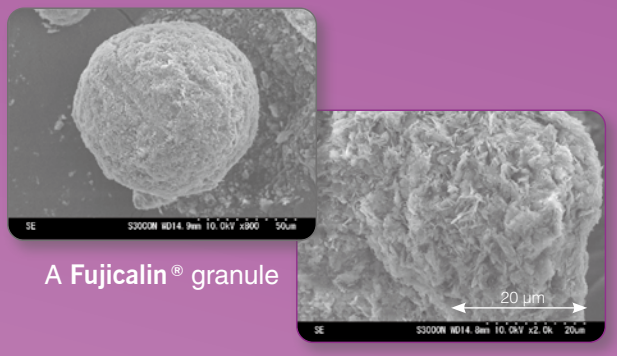
Anhydrous dibasic calcium phosphate (JP)
Anhydrous dibasic calcium phosphate (USP)
Calcium hydrogen phosphate, anhydrous (EP)

The core benefits of **Fujicalin®** as an excipient

Fujicalin® - The Unique DCPA

Fujicalin® is a *dibasic calcium phosphate anhydrous* (DCPA) designed to function as a direct compression excipient. It has exceptional flow and compression characteristics while maintaining the ability for rapid disintegration. The key to Fujicalin®'s superior performance is the highly specialized and proprietary manufacturing process that yields unique primary particles.

Electron micrographs of **Fujicalin®**



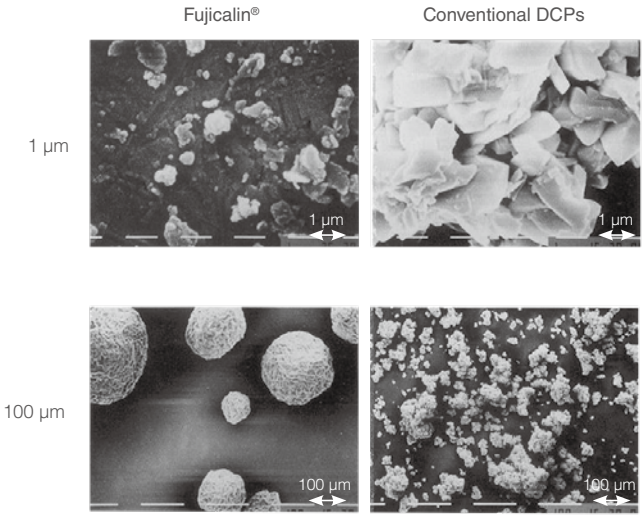
A **Fujicalin®** granule

Internal structure of **Fujicalin®**

Fujicalin® vs Conventional DCPs

Fujicalin®'s patented manufacturing process yields porous spheres with high specific surface area. Fujicalin® is totally synthetic and ideally suited for direct compression formulations, especially those involving difficult-to-compress materials like oily actives. It can be used to assist flow, reduce tablet weight variation and improve content uniformity. Fujicalin®'s density facilitates the design of smaller tablets. It can also be used as a partial or total replacement for *microcrystalline cellulose* (MCC).

Electron Microphotograph of **Fujicalin®** and Conventional Dibasic Calcium Phosphates

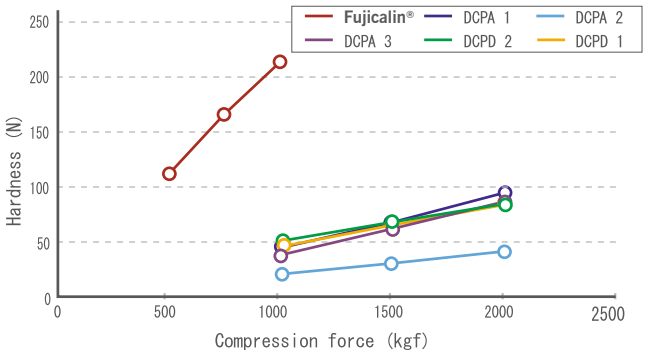


Comparison of properties among **Fujicalin®**, conventional DCPA and DCPD

Property	DCPA		DCPD
	Fujicalin®	Conventional	
Mean particle size (μm)*	120	45	127
Bulk density, loose (g/mL)	0.46	0.76	0.83
Bulk density, tapped (g/mL)	0.54	0.78	0.91
Angle of repose (°)	30	42	35
BET specific surface area (m^2/g)	40	0.7	0.57
Oil adsorption capacity (mL/g)	1.1	0.4	0.2
Water adsorption capacity (mL/g)	1.2	0.5	0.2

*Sieve method. DCPA: dibasic calcium phosphate anhydrous, DCPD: dibasic calcium phosphate dihydrate.

Comparison of tablet hardness with other available DCPA's



Fujicalin®'s high specific surface area contributes to higher tablet hardness at low compression forces.

Advanced Applications

Fujicalin® is recommended for preparing **probiotic** formulations. With Fujicalin®, probiotic tablets can be produced by direct compression at low compression forces which leads to increasing cell viability. Commercially available probiotic products using Fujicalin® can be stored at room temperature with a shelf life of up to 3 years using normal bottle packaging.

Fujicalin® is an ideal carrier for *self-emulsifying drug delivery systems* (**SEDDS**), liquisolid systems, as well as *hot melt extrusion* (**HME**) to improve tablet properties and bioavailability of poorly water soluble drugs. Fujicalin® has also been commercially used as primary excipient in **roller compaction**. Fujicalin® is able to facilitate fast disintegration of tablets and is recommended for fast releasing SEDDS applications.

Fujicalin® Features

- Highly compressible, and produces harder tablets than other directly compressible conventional excipients
- Easy blending and excellent flowing properties due to its spherical shape, which creates less friction
- Works with other disintegrants to promote rapid disintegration regardless of tablet hardness
- Fujicalin® granules have a smooth surface and are less abrasive compared to other DCPAs and DCPDs
- High degree of porosity is retained even under high pressure, resulting in excellent oil adsorbing capability
- Approved for pharmaceutical and food excipient use allowing versatile applications

Pharmacopoeia & Regulatory

Fujicalin® conforms to USP, EP, and JP.
Anhydrous dibasic calcium phosphate or calcium hydrogen phosphate, anhydrous is also applicable for food use.
It is US DMF Type IV filed and listed as GRAS (Generally Recognized As Safe).

Further reading

1. Prajapati ST. *et al.*, Formulation and Evaluation of Liquisolid Compacts for Olmesartan Medoxomil. J Drug Deliv. 2013: 2013:ID 870579
2. Sohn Y. *et al.*, Development of self-microemulsifying bilayer tablets for pH-independent fast release of candesartan cilexetil. Pharmazie. 2012; 67:917-24
3. Hentzschel CM. *et al.*, Comparison of traditional and novel tableting excipients: Physical and compaction properties. Pharm Dev Technol. 2012; 17:649-53
4. Kang MJ. *et al.*, Immediate release of ibuprofen from Fujicalin®-based fast-dissolving self-emulsifying tablets.a Drug Development and Industrial Pharmacy. 2011; 37:1298-305
5. Hiroshi S. *et al.*, Formulation of lactic acid bacterium dosage form -Challenging for the unmanned direct compression. Pharm Tech Japan. 2009; 24: 27-32

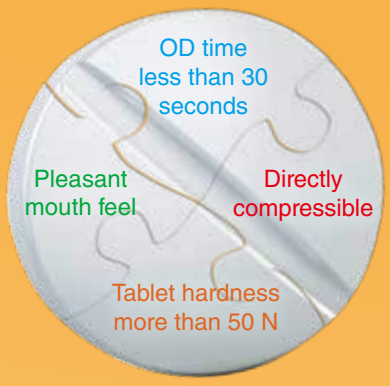
Fast Melt Tablets Made Easy!

F-MELT®

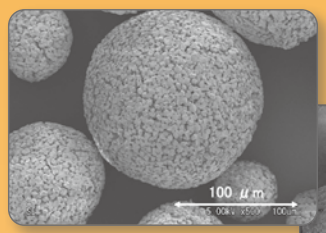
"The Challenges and Opportunities of ODTs"

A patient-centric drug delivery system to deliver specialized medicines to the aging population is very critical to any pharmaceutical drug development program. Difficulty in swallowing is a major problem of the aged, patient populations with specific diseases. One of the best choices to overcome the problem associated with swallowing difficulties is an orally disintegrating tablet (ODT) drug delivery system. For ODTs, the key challenges are producing tablets with optimum tablet hardness, rapid disintegration and overcoming the bitter taste exhibited by many actives. F-MELT® addresses these challenges with ease and offers pharmaceutical companies the opportunity to take products to market quickly.

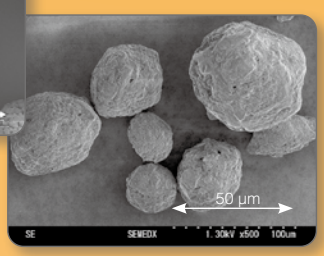
The core benefits of F-MELT® as an excipient



Electron micrographs of **F-MELT®**



F-MELT® F1 granules



F-MELT® Type C granules

F-MELT®

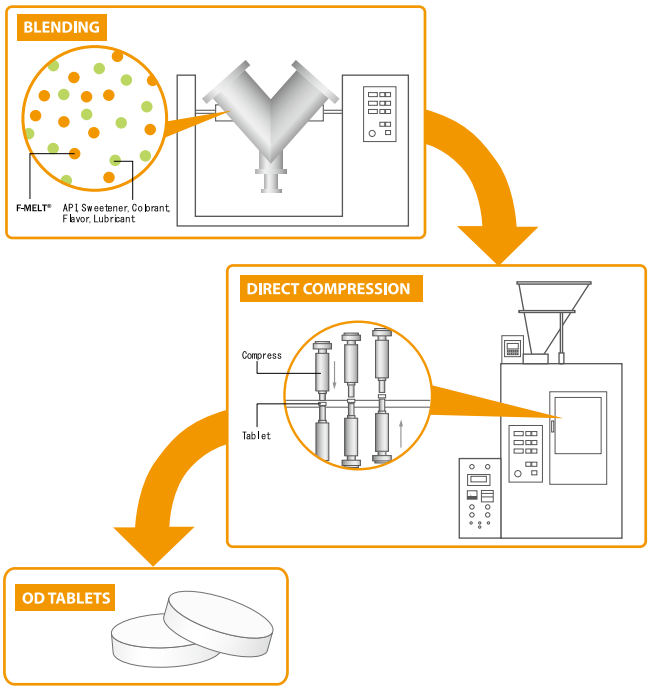
F-MELT® is a proprietary, co-spray dried excipient launched by Fuji Chemical in 2005. F-MELT® is designed not only for manufacturing ODTs and tablets that dissolve fast in the oral cavity without the need of water, but also as an excellent excipient for soft chewable tablets. It is suitable for manufacturing directly compressible ODTs simply by blending with active pharmaceutical ingredients (APIs) and lubricants.

Physical Properties and Grades of F-MELT®

Type	Type C	Type M	F1
Appearance	White to pale yellow powder		
Loose bulk density (g/ml)	0.54	0.56	0.50
Tapped bulk density (g/ml)	0.65	0.65	-
Mean particle size distribution (μm)	121	122	139
Angle of repose (°)	34	33	31
Ingredients	D-Mannitol, Xylitol, MCC, Crospovidone, **Fujicalin®**	D-Mannitol, Xylitol, MCC, Crospovidone, **Neusilin®**	Waxy rice starch, MCC, **Fujicalin®**

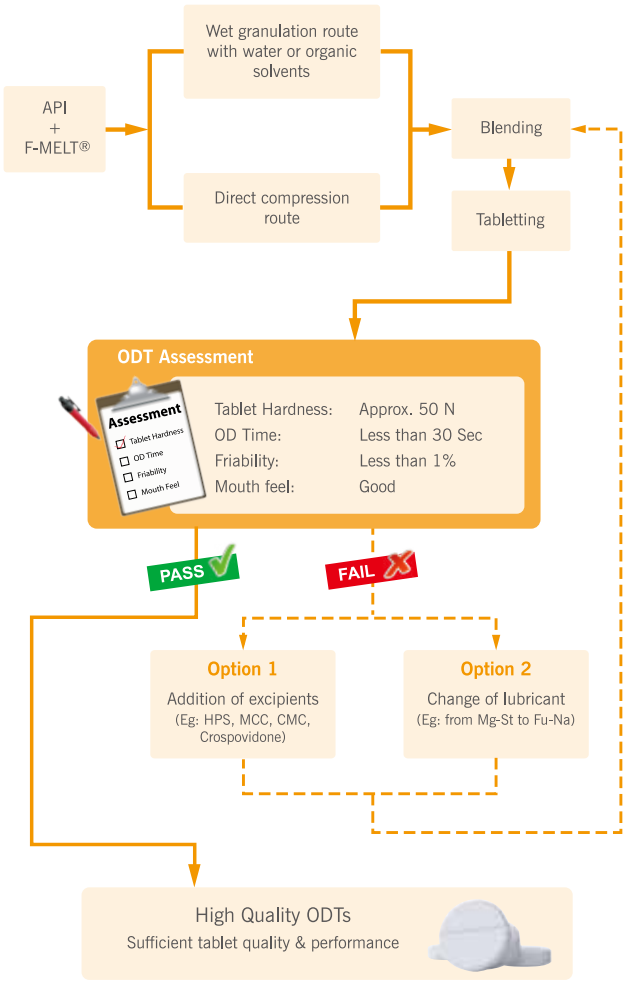
Manufacturing Process of ODT with F-MELT®

Manufacturing ODTs using **F-MELT®** is simple—blend F-MELT® with APIs and lubricant and prepare tablets by direct compression. In addition, flavors, colorants, sweeteners, etc., could be incorporated for improved patient-compliance.



Strategy for Preparing High Performance F-MELT® Tablets (Type C & Type M)

F-MELT® is a directly compressible excipient. Depending on the actives, ODTs can also be prepared with F-MELT® through wet granulation and suitable solvents. Furthermore, if the ODT quality does not meet requirements, formulators can improve the quality by adding other excipients and/or changing the lubricant.



Grades

Grade	Characteristic
Type C	Pharmaceutical and nutraceutical applications
Type M	Pharmaceutical applications
F1	Nutraceutical and dietary supplement applications

*Please check regulatory status of each component in respective countries.

Pharmacopoeia & Regulatory

F-MELT® is manufactured under strict quality control at Fuji's cGMP certified facilities. Type C conforms to Japanese Pharmaceutical Excipients and all components meet USP-NF, JP, and EP. US DMF Type IV field. Type M conforms to Japanese Pharmaceutical Excipients and all components meet USP-NF and JP/JPC. F1 ingredients are food grade excipients.

Safety

F-MELT® Type C and Type M

The components of F-MELT® Type C and M are safe with no reports of adverse reactions when used as excipient in pharmaceutical applications.Type C is also suitable for nutraceutical/food* applications. The components of Type C have E-numbers (EU Food Directive), and are listed in USA CFR 21 and the list of Acceptable Non-Medical Ingredients in Canada.

*Please check regulatory status of each component in respective countries.

F-MELT® F1

F-MELT® F1 is for nutraceutical/food applications.

TSE/BSE, Non-GMO, Allergen free certificates are available upon request. F-MELT® does not contain any residual organic solvent.

F-MELT® Features

- Ready to use excipient system for ODTs
- OD time less than 30 seconds
- Spherical particles with high flowability
- Directly compressible
- API loading more than 50% possible
- Tablet hardness more than 50N possible with little or no sticking/capping
- Pleasant mouth feel
- Easy handling and storage of ODTs with low friability
- No special equipment required for tabletting
- No royalty or license fees required

Further reading

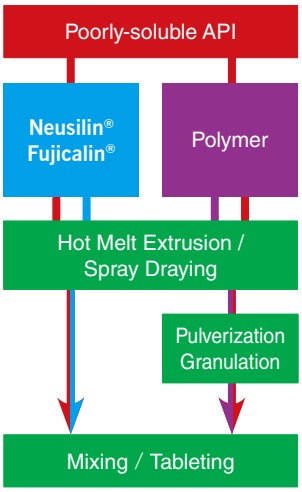
Machimura H. F-MELT® -An ideal excipient for orally-disintegrating tablet formulations. JSPME, 2011, Vol.20(1) p26-32. <In Japanese>

Bowles, B.J., Dziemidowicz, K., Lopez, F.L. et al. AAPS PharmSciTech (2018) 19: 2598. https://doi.org/10.1208/s12249-018-1090-4

Dziemidowicz, K., Lopez, F.L., Bowles, B.J. et al. AAPS PharmSciTech (2018) 19: 2646. https://doi.org/10.1208/s12249-018-1104-2

Solid Dispersion Application of **Neusilin®** and **Fujicalin®**

Turning the active into an amorphous state is one method to improve the solubility of poorly soluble APIs. Neusilin® and Fujicalin®, which are porous, inorganic excipients, can stabilize the amorphous state of APIs. They can be used as an inert carrier to prepare amorphous solid dispersion via *spray drying* (SD) or *hot melt extrusion* (HME).



Hot Melt Extrusion Applications of **Neusilin®** and **Fujicalin®**

Neusilin® HME Powder

Fujicalin® HME Powder

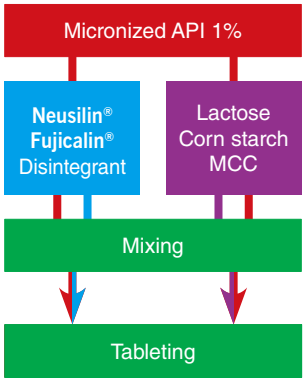
The *hot melt extrusion* (HME) method micronizes the API and carrier, then it softens/melts the active and disperse it over the carrier.

A polymer is typically used as a carrier, and pulverization is also required since rigid pellets are obtained after the HME process. On the other hand, pulverization is not required when Fujicalin® and Neusilin® are used as carriers. Fujicalin® and Neusilin® serve as adsorbents and maintain their flowability even after the HME processing.

Homogeneity Improvement with Fujicalin®

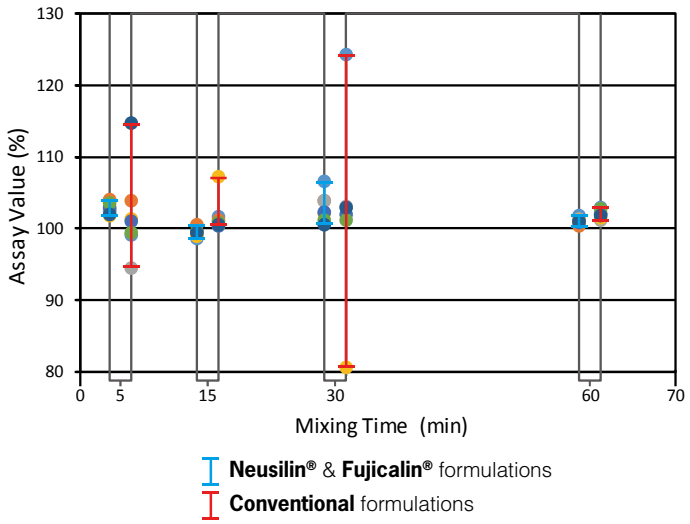
Direct compression offers a cost advantage. However, the powder properties of the active can complicate manufacturing. The attainment of batch homogeneity is crucial, especially when the API ratio is relatively small.

Fujicalin® improves the homogeneity issue, and its exceptional flowability and compressibility can solve tableting issues. If small amount of Neusilin® is added into the formulation, the tabletting issue is solved further more, as shown in the graphs below.

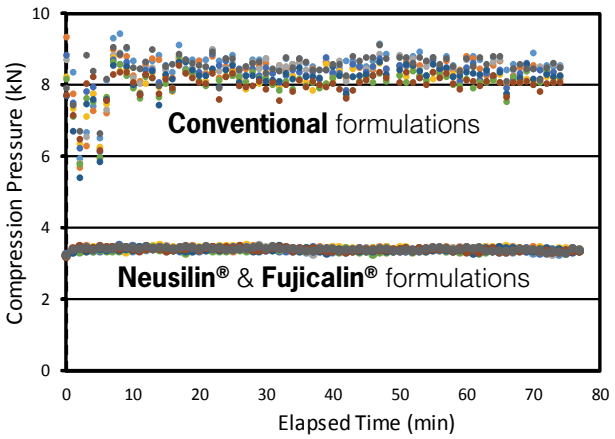


A **Neusilin®** and **Fujicalin®** formulations achieve homogeneity in a shorter amount of time, with minimal tablet weight variation and very low constant compression pressure.

Homogeneity of Neusilin® and Fujicalin® formulations vs. conventional formulations



Compression Pressure of Neusilin® and Fujicalin® formulations vs. conventional formulations



Reference

M. Maniruzzaman et al., International Journal of Pharmaceutics, 496(2015)42-51

Fuji Chemical Group

JAPAN

API & Pharmaceutical Division
(Tokyo office, International Business)

Shibakoen Ridge Building 2nd Floor, 1-8-21 Shibakoen,
Minato-ku, Tokyo 105-0011, Japan
T: +81-3-3437-2350 F: +81-3-3437-2347

Headquarters and Plant

55 Yokohoonji, Kamiichi-machi,
Nakaniikawa-gun, Toyama 930-0355, Japan
T: +81-76-472-2323 F: +81-76-472-2330

Gohkakizawa Plant

1 Gohkakizawa, Kamiichi-machi,
Nakaniikawa-gun, Toyama 930-0405, Japan
T: +81-76-472-5538 F: +81-76-472-5342

Namerikawa Plant

183-5 Yasuda, Namerikawa-shi,
Toyama 936-0825, JAPAN
T: +81-76-476-0881 F: +81-76-476-0885

UNITED STATES

Fuji Chemical Industries USA, Inc.

3 Terri Lane, Unit 12
Burlington, NJ 08016
United States of America
T: +1-609-386-3030 F: +1-609-386-3033
www.fujichemicalUSA.com
contact@fujichemicalUSA.com

INDIA

AstaReal (India) Private Limited

120, Ackruti Star, Central Road,
Opp. Akruti Centre Point, MIDC, Andheri (E),
Mumbai 400093, India
T: +91 22 62369998

EUROPE

Fuji Chemical Industries (Sales Office)

Forumvägen 14, Level 16, 131 53, Nacka, SWEDEN
T: +46 72-858-71-93

Affiliated Corporations

JAPAN

AstaReal Co., Ltd.

Shibakoen Ridge Building 8th Floor, 1-8-21 Shibakoen,
Minato-ku, Tokyo 105-0011, Japan
T: +81 3-3437-2353 F: +81 3-3437-2348
www.astareal.com

SWEDEN

AstaReal AB (Sales and Marketing)

Forumvägen 14, Level 16, 131 53, Nacka, Sweden
T: +46 8-570-139-50 F: +46 8-570-139-51
www.astareal.se
info@astareal.se

AstaReal AB (Production Facility)

Britt-Louise Sundells gata 7-9, 134 50, Gustavsberg, Sweden

UNITED STATES

AstaReal, Inc. (Sales and Marketing)

3 Terri Lane, Unit 12
Burlington, NJ 08016
United States of America
T: +1 609-614-6904 F: +1 609-386-3033
www.astarealUSA.com
contact@astarealUSA.com

AstaReal, Inc. (Production Facility)

7761 Randolph Rd NE,
Moses Lake, WA 98837
United States of America
T: +1 509-855-4370 F: +1 509-765-9073

SINGAPORE

AstaReal Pte. Ltd.

T: +65 6222-1778 F: +65 6222-1779
contact@astareal.sg

Solving Puzzles since 1946

Creativity and Contribution

Fuji Chemical Industries Co., Ltd.

API & Pharmaceutical Business Division:
Shibakoen Ridge Building 2nd Floor, 1-8-21 Shibakoen,
Minato-ku, Tokyo 105-0011, Japan
Telephone: +81-3-3437-2350 Fax: +81-3-3437-2347
E-mail: pharma@fujichemical.co.jp

Headquarters and Plant:
55 Yokohoonji, Kamiichi-machi, Nakaniikawa-gun, Toyama 930-0355, Japan
Telephone: +81-76-472-2323 Fax: +81-76-472-2330

www.fujichemical.co.jp

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