Fuji Chemical Industries Co., Ltd.

Fuji Chemical Technical Newsletter

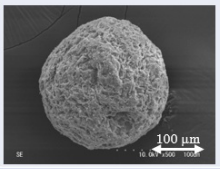
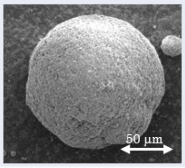
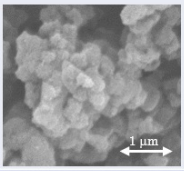
Application of porous inorganic excipients to solid dispersions

The use of direct compression continues to increase due to then increasing number of formulations with heat & moisture sensitive active pharmaceutical ingredients (APIs).
However, APIs which have been finely ground and micronized in order to improve solubility frequently cause various problems for direction compression.

In this technical newsletter, we shall show you how Fuji Chemical's problem-solving excipients can help you to achieve higher solubility along with uniformity of blending using the direct compression approach.

The number of poorly soluble drug candidates has been increasing in recent years and a range of solubilizing techniques to improve their absorption are under investigation. Generally, approaches for improving the solubility of poorly soluble drugs include either increasing the surface area of the drug or changing the form of the drug to a more soluble one. Methods such as pulverization increase the surface area of the drug, thus increasing the area in contact with the solvent and thus the rate of solubilization. More soluble forms of the drug can be achieved by means of a non-crystalline solid dispersion and other methods such as co-crystallization have also recently come into practical use.
As a company whose key competence is spray drying, we are actively engaged in finding solutions for improving the solubility of poorly soluble spray-dried drugs using spray drying technologies. Our company also manufactures and sells the porous inorganic excipients Neusilin® and Fujicalin® (**Table 1**).
In this report we describe examples of applications of our company's porous inorganic excipients in solid dispersions of poorly soluble drugs

Table 1. Fujicalin SG and Neusilin US2 and UFL2

Product name	Fujicalin® SG	Neusilin® US2	Neusilin® UFL2
Generic name	Calcium phosphate anhydrous	Magnesium aluminometasilicate	
SEM image			
Mean particle diameter (µm)	120	106	3.1
BET specific surface area (m^2/g)	40	300	300
Pore volume (cm^3/g)	0.25	1.74	1.50
Oil absorption capacity (ml/g)	1.1	2.7-3.4	2.7-3.4

*Physical property values are reference values.

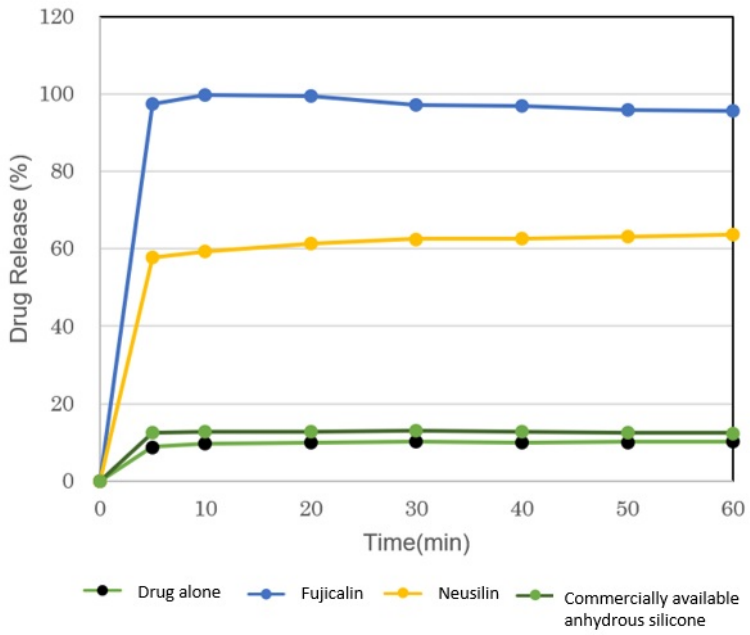
Example application using spray drying

We investigated differences in solubility as a result of the addition of inorganic excipients, using Indomethacin as a model drug.
A 1:1 mixture of indomethacin and an inorganic excipient dispersed in ethanol were spray dried using a BÜCHI B-191 to formulate a spray-dried product. The inorganic excipients used were the porous excipients Fujicalin® and Neusilin® UFL2, as well as commercially available anhydrous silicic acid.

Figure 1 shows the results of *in-vitro* dissolution results. The dissolution medium used in these *in-vitro* dissolution test was 500 mL of purified water and the paddle method (250 rpm).

The porous inorganic excipients Fujicalin® and Neusilin® both increased the solubility compared with indomethacin alone or with commercially available anhydrous silicic acid alone.

Figure 1. Solubility test results (using amounts equivalent to indomethacin 50 mg)



Example application using hot melt extrusion (HME)

Professor Douroumis of the University of Greenwich has carried out tests of Fujicalin® and Neusilin® using the hot melt extrusion (HME) method, as described below.1)

Formulation trial in Hot melt Extrusion (HME) using Fujicalin®

Tests were conducted to investigate the differences between Fujicalin®, a porous form of dibasic calcium phosphate anhydrous (DCPA), and commercially available DCPA, using chlorthalidone as the model drug. Chlorthalidone and DCPA were mixed in a 60:40 ratio and treated at 200ºC in a Thermo Fisher EuroLab16 (Twin screw Hot Melt Extrusion) to formulate an amorphous solid dispersion.

Figure 2 shows the appearance of the solid dispersions formulated by HME. The solid dispersion formulated with commercially available DCPA formed solid pellets, whereas the solid dispersion formulated with Fujicalin® formed a powder with good fluidity.
The use of Fujicalin® made the HME treatment process easier and enabled the crushing process that normally follows to be omitted. By using Fujicalin® we have found free flowing granules which in the case of conventional DCPA or another polymer generally produced extrudes. Generally, extrudes required a cooling process, cutting and milling process and such down-stream processes are very time consuming. Sometime with such extrudes it creates a problem in longer disintegration time of the tablet due to the hard nature of milled granules. With the use of a porous excipients like Fujicalin® and Neusilin®, down-stream processes can be minimized. Here the role of a porous excipient is to stabilize the amorphous form of the API since the amorphous state of the API is in a metastable stage and it usually converts into a crystalline state in the presence of moisture. While porous excipients stabilize the amorphous state due to its moisture adsorption property and higher surface area.

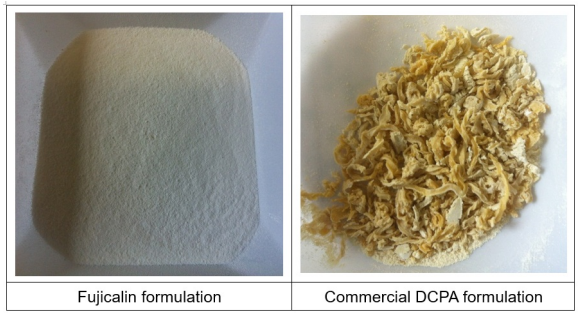


Figure 2. Appearance of solid dispersions obtained by HME

Formulation trial in Hot melt Extrusion (HME) using Neusilin® US2[1)]

Solid dispersions were formulated using indomethacin (IND) as the model drug. Indomethacin and Neusilin® were mixed in 20:80, 30:70 and 40:60 ratios and solid dispersions were formulated by HME under the same conditions as for the Fujicalin® tests.
Figure 3 shows X-ray diffraction spectra of the solid dispersions formulated by HME (EXT products) and physically mixed products (PM products). Indomethacin peaks are evident in the physically mixed products, but the solid dispersions formulated by HME exhibit a halo pattern, indicating that all the formulae are non-crystalline and converted into amorphous state after the HME process in presence of Neusilin®

Figures 4 and **5** show the results of *in-vitro* dissolution testing. The solubility tests were conducted in accordance with the indomethacin USP monograph.
Treatment with HME increased the elution rate and this effect was more pronounced when the proportions of Neusilin® was higher.

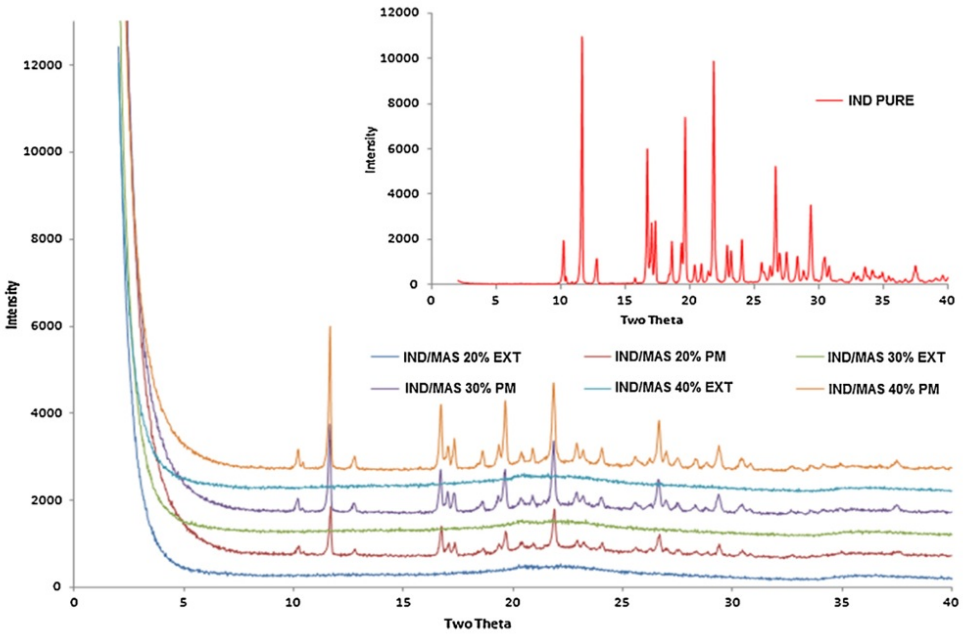


Figure 3. XRD[1)] of solid dispersions (EXT products) and physically mixed products (PM products)

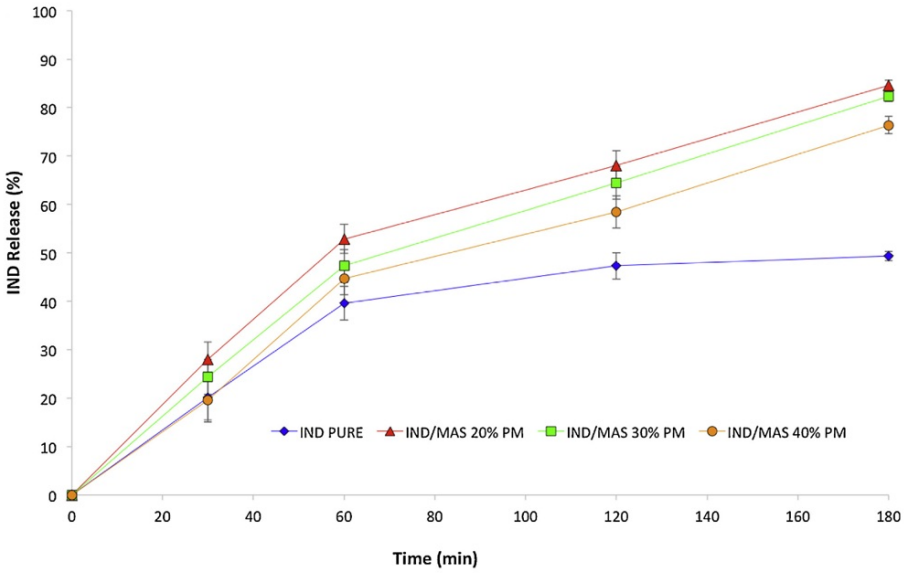


Figure 4. Results of *in-vitro* dissolution testing of physically mixed products (using amounts equivalent to indomethacin 100 mg)[1)]

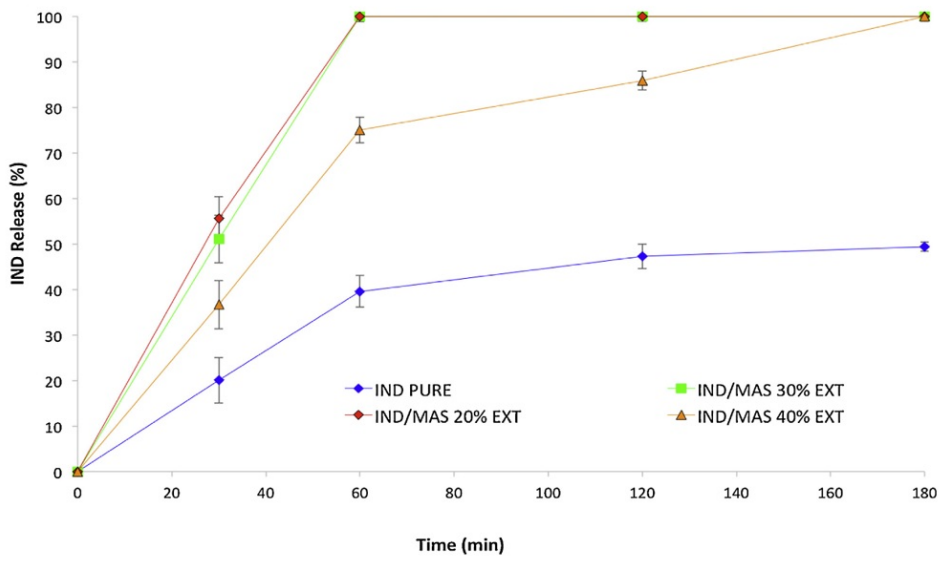


Figure 5. Results of *in-vitro* dissolution test of solid dispersions (EXT products) (using amounts equivalent to indomethacin 100 mg)[1)]

Conclusion

In this report we described examples of the application of porous inorganic excipients- Neusilin® and Fujicalin® to amorphous solid dispersion preparation, one method of improving the solubility of poorly soluble drugs and demonstrated new possibilities for the use of these materials. We have conducted formulation development trial in spray drying and hot melt extrusion (HME) process and found promising results in solubility enhancement of poorly soluble drugs in both solid dispersion technology using inorganic porous excipient like Neusilin® and Fujicalin®.

At Fuji Chemical, in addition to **Neusilin®** and **Fujicalin®**, we are also developing excipients with an even greater specific surface area than that of **Neusilin®**. We will continue to propose more applications for these porous inorganic excipients, in an effort to make even a small contribution to drug development.

*References 1) M. Maniruzzaman et al.; Int. J. Pharm. 496 (2015) 42-51

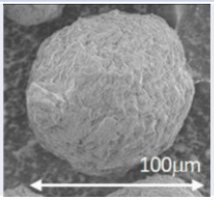
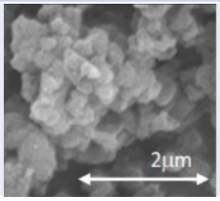
About Fuji Chemical's problem-solving excipients

Neusilin®

Neusilin® is an amorphic magnesium aluminometasilicate and magnesium aluminosilicate synthesized using Fuji Chemical's own technology. It also has physiochemically superior formulation properties such as the capacity to absorb oil/water, excellent compressibility and is widely used as a binding agent, disintegration auxiliary agent, anticaking agent, flowability improving agent and adsorption powderizing agent for quality improvement.

Fujicalin®

Fujicalin® is an anhydrous dibasic calcium phosphate designed to exhibit useful functions as an excipient in direct compression. It possesses excellent flowability and compressibility, as well as the ability to rapidly disintegrate when used in combination with disintegrating agents as an auxiliary disintegration agent.

	Fujicalin® SG	Neusilin® UFL_2
Average Particle Size (μm)	113	1.6
Angle of Repose (°)	30	45
Bulk Density (g/ml)	0.43	0.08
Photograph of Appearance (SEM)		

Please contact us for more information. Sample of **Fujicalin**® and **Neusilin**® are available upon request.

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