Fuji Chemical Industries Co., Ltd.

Fuji Chemical Technical Newsletter

Excipients for Direct Compression—
Content Uniformity in Directly Compressed Formulations

The use of direct compression continues to increase due to permitting formulations with heat & moisture sensitive active pharmaceutical ingredients (APIs).
However, APIs which have been finely ground for increased 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 uniformity in the blending and direct compression of formulas containing finely-ground APIs.

Using acetaminophen (hereinafter abbreviated as AA) ground with a jet mill (average particle size 4 μm), we examined the low-dose formulations' blend homogeneity, the flowability of the mixture, the tablets' variations in mass, and the content uniformity of the tablets.

<Blending Experiment>
With Å of 0.1 wt% and 1.0 wt%, the Fujicalin®, Neusilin®, and carboxymethyl starch sodium (hereinafter abbreviated as CMS) formula as shown in **Table 1**, and the samples excluding magnesium stearate (hereinafter abbreviated as Mg-St) were blended in a V-type mixer for 60 minutes as shown in the flowchart of **Figure 1**.

Table 1: Formula Used in Experiment

Experiment Number	Experiment 1		Experiment 2		Experiment 3	
Formula	W/W (%)	Supplied Amount (g)	W/W (%)	Supplied Amount (g)	W/W (%)	Supplied Amount (g)
AA Ground by Jet Mill	1.0	80.0	1.0	80.0	0.1	8.0
Fujicalin SG	96.0	7680.0	95.0	7600.0	95.9	7672.0
CMS	2.0	160.0	2.0	160.0	2.0	160.0
Neusilin UFL2			1.0	80.0	1.0	80.0
Mg-St	1.0	80.0	1.0	80.0	1.0	80.0
Total	100.0	8000.0	100.0	8000.0	100.0	8000.0

Similarly, for the comparisons, a standard formula consisting of lactose (200 Mesh), corn starch (hereinafter abbreviated as CS), and crystalline cellulose (hereinafter abbreviated as MCC) as shown in **Table 2**, and the samples excluding Mg-St were blended in a V-type mixer for 60 minutes as shown in the flowchart of **Figure 2**.

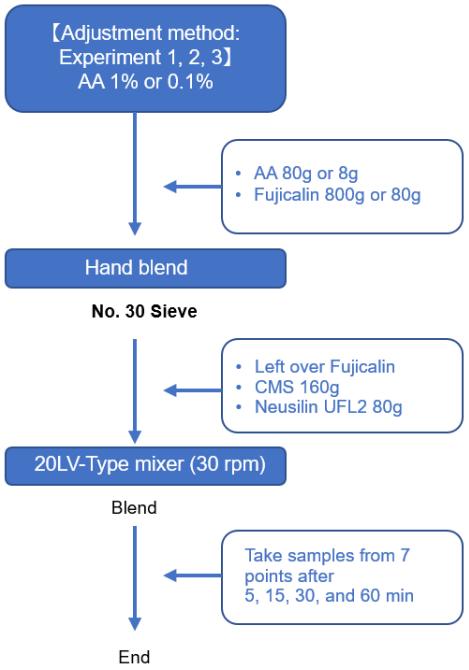


Figure 1: Flowchart for the Blending of Materials Used in the Experiments

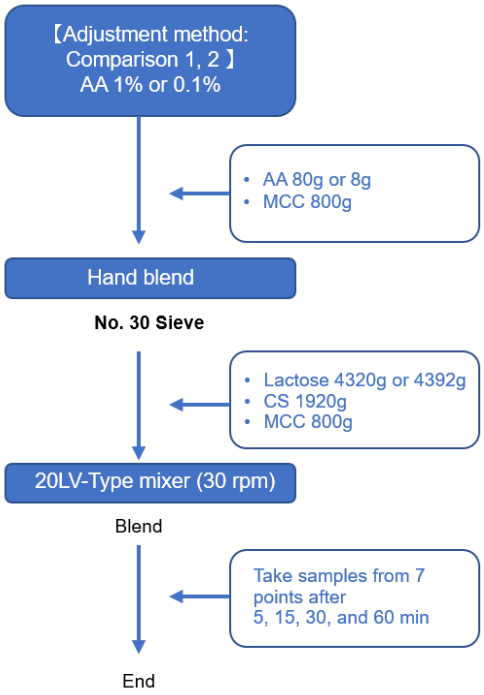


Figure 2: Flowchart for the Blending of Materials Used in the Comparisons

Table 2: Formula Used in Comparison

Experiment Number	Comparison 1		Comparison 2	
Formula	W/W (%)	Supplied Amount (g)	W/W (%)	Supplied Amount (g)
AA ground by jet mill	1.0	80.0	1.0	80.0
Lactose (200M)	54.0	4320.0	54.9	4392.0
CS	24.0	1920.0	24.0	1920.0
MCC	20.0	1600.0	20.0	1600.0
Mg-St	1.0	80.0	1.0	80.0
Total	100.0	8000.0	100.0	8000.0

Samples of the mixture were taken from 7 points at 5, 15, 30, and 60 minutes after the blending began. The sampling points are shown in **Figure 3**.

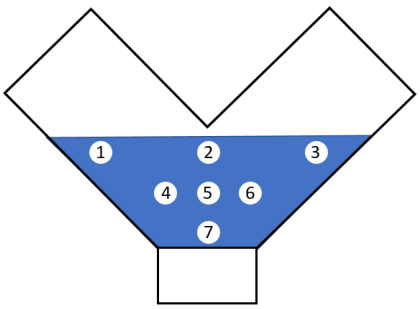


Figure 3: Sampling Points

The changes in the quantitative values due to the blending experiments are shown in **Figures 4–8**. Even with an AA content of 0.1 wt%, content uniformity could be confirmed after 30 minutes of blending. With an AA content of 1.0 wt%, content uniformity could be maintained after 30 minutes of blending if only **Fujicalin**® was used, and when used in combination with **Neusilin**®, content uniformity could be maintained even when the blending time was shortened further. Even in the standard formula of the comparisons, we found that 60 minutes of blending for 1.0 wt% AA, and 30 minutes of blending for 0.1 wt% AA was sufficient.

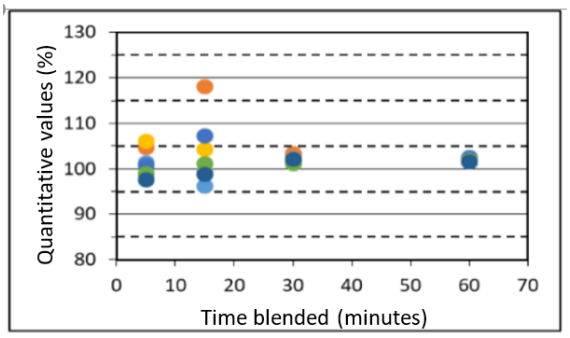


Figure 4. Experiment 1 (Blending)

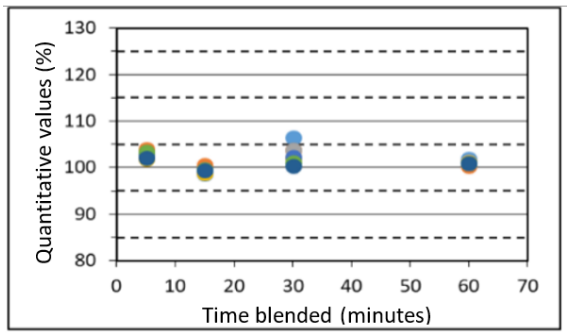


Figure 5. Experiment 2 (Blending)

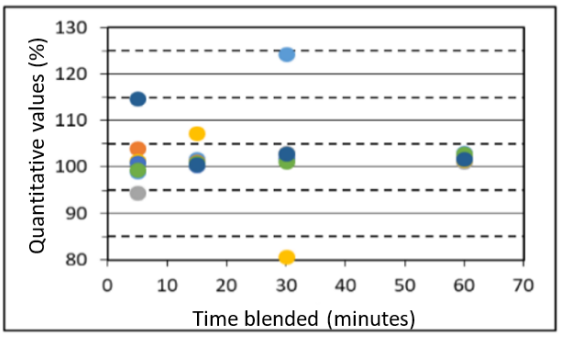


Figure 6: Comparison 1 (Blending)

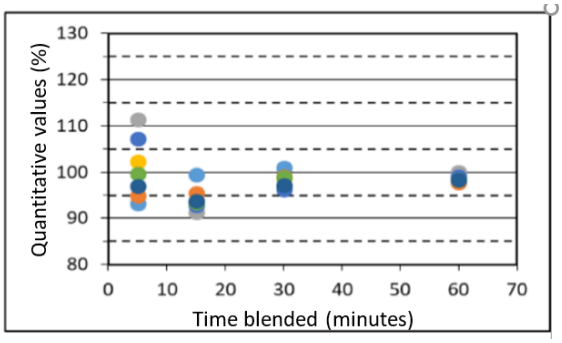


Figure 7: Experiment 3 (Blending)

Using FLODEX, the orifice flowability and the angles of repose of the mixtures were measured. Those results are shown in **Table 3**. From these results, it was confirmed that the flowability of the mixtures of Experiments 1–3 were good. We believe that this is due to AA adhering to the surface of **Fujicalin®** and contributing to the improvements in blend homogeneity.

Table 3: Formula Used in Comparison

	Experiment 1	Experiment 2	Comparison 1	Experiment 3	Comparison 3
Orifice Flowability	4	9	22	6	24
Angle of Repose (°)	40	40	51	40	51

Compression Experiment

Mg-St was mixed to the samples made in the blending experiment in accordance with the flowchart of **Figure 9**, then compressed. At this time, changes in compacting pressure and variations in mass during compression, as well as the content uniformity of the samples were measured. Kikusui Seisakusho Co., Ltd.'s VIRGO was used to compress tablets measuring φ9 x 13R, at 300 mg/tablet, and a set hardness of 70 N with a 9-rack, 30 rpm, open feeder. Samples of the tablets were taken immediately after beginning, after compressing 5,000 tablets, 10,000 tablets, and 15,000 tablets, and before ending compression.

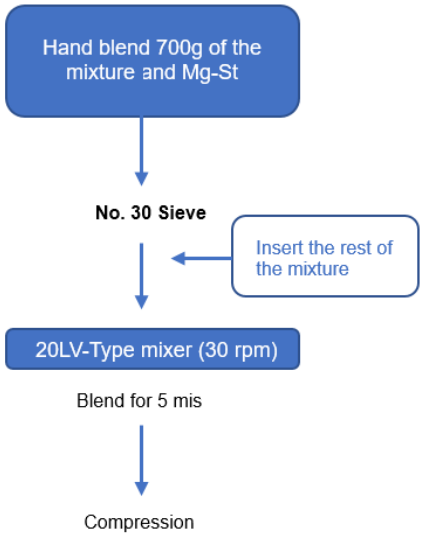


Figure 9: Flowchart of Adjustments to Compression

Changes in compacting pressure during compression are shown in **Figures 10–14**. Additionally, **Figures 15 & 16** show the variations in tablet mass during compression. From these results, it was confirmed that by using our company's additives, compression can result in less variation in the filling of the dies, and lower, more consistent compacting pressure with less variations in mass. We believe this to be due to the flowability of the mixture. And although the compacting pressure in Experiment 2 is lower than that of Experiment 1, we believe this is due to the **Neusilin®** acting as a auxiliary molding agent.

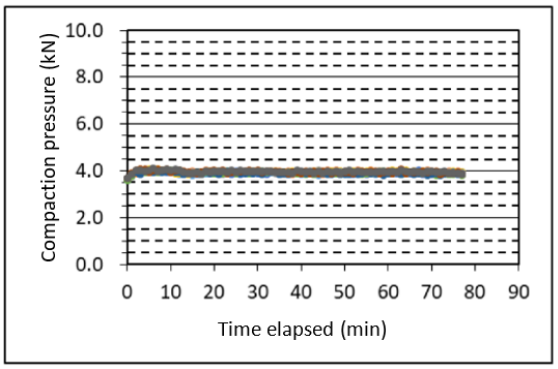


Figure 10: Changes in Compaction Pressure for Experiment 1

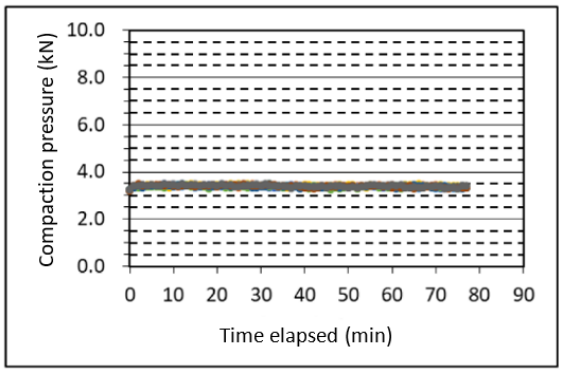


Figure 11: Changes in Compaction Pressure for Experiment 2

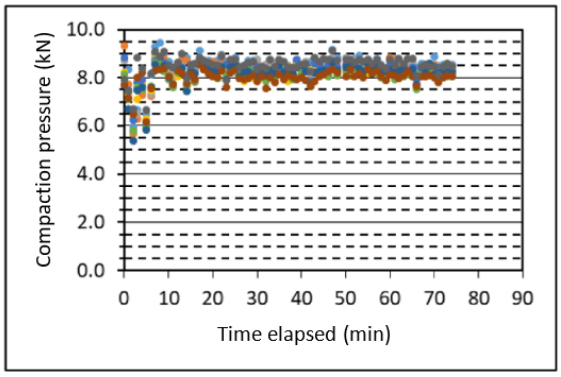


Figure 12: Changes in Compaction Pressure for Comparison 1

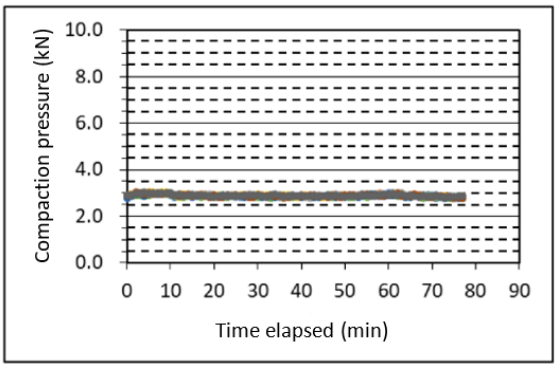


Figure 13: Changes in Compaction Pressure for Experiment 3

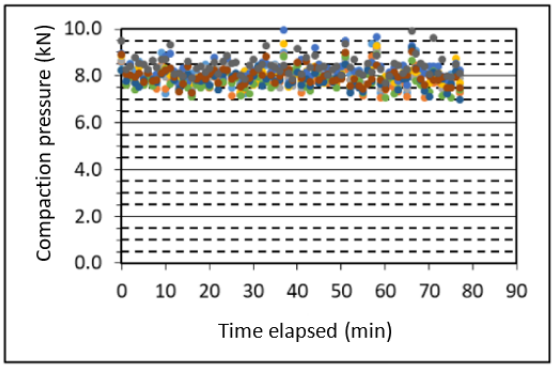


Figure 14: Changes in Compaction Pressure for Comparison 2

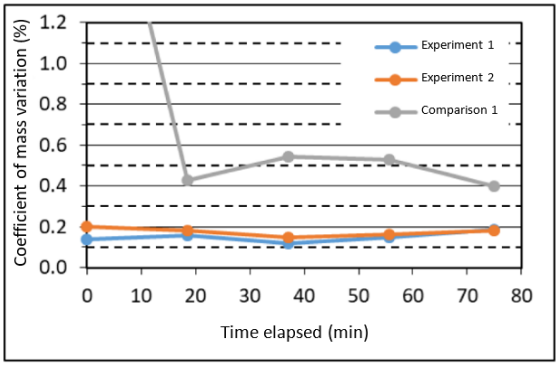


Figure 15: Variations in Tablet Mass During Compression (AA 1.0 wt%)

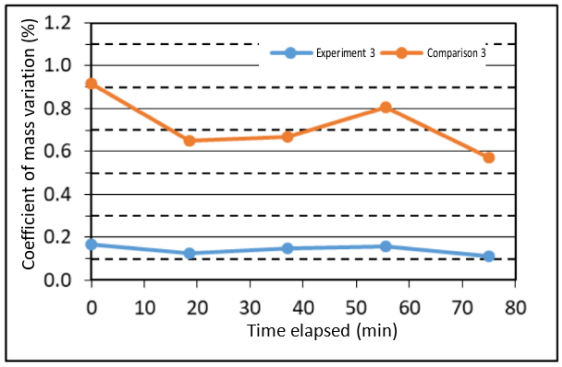


Figure 16: Variations in Tablet Mass During Compression (AA 0.1 wt%)

Next, the content uniformity tests of the tablets sampled immediately after the start, after the compression of 10,000 tablets and before the end were conducted. These values are shown in **Table 4**. The time-dependent changes in these values are thought to be due to the variations in mass. From these results, it was confirmed that when using formulas containing our company's additives, satisfactory content uniformity could be maintained through compression.

	Immediately After Beginning	After 10000 Compressions	Just Before Ending
Experiment 1	2.66	2.92	3.94
Experiment 2	2.94	2.35	1.68
Comparison 1	12.36	5.69	4.81
Experiment 3	1.96	1.67	3.52
Comparison 2	6.14	4.87	3.29

Table 4: Values Determined by the Tablet Content Uniformity Tests

Summary

In this experiment, we found that by utilizing the characteristic particle properties of **Fujicalin®** and **Neusilin®** in the blending and direct compression of low-dose formulations containing acetaminophen ground with a jet mill, we were able to achieve consistent compressions, as well as satisfactory blend homogeneity and content uniformity.
We hope the information in this paper will be in future dry direct compressions.

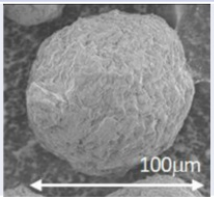
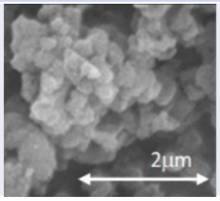
About Fuji Chemical's problem-solving excipients

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 and compression moldability, 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 compression moldability, 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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