Study of direct compression coverage in view of design space -Ceolus™ UF grades-

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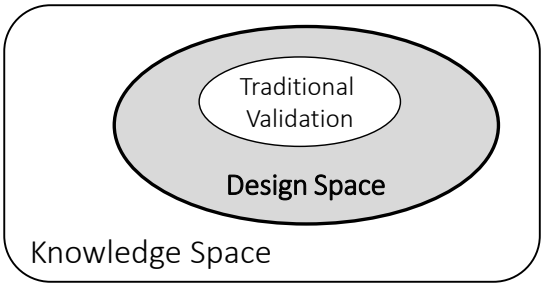
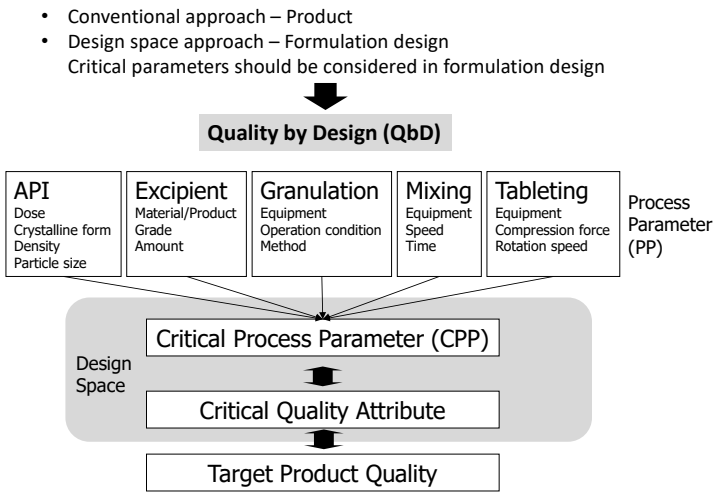
1. What is the design space?

The design space (DS) is a multidimensional combination and interaction of input variables (e.g., properties of raw materials) and process parameters that have been proven to ensure the quality of drug products. Operation within the DS is not considered a change, therefore the DS is proposed by the applicant, and evaluated and approved by the regulatory authority. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommends the DS as a prerequisite for the production of drug products to improve product quality.

1st to 3rd Study Forum for Standardized Formulation





2. Purpose of this study

Our previous research was carried out on a laboratory scale (small rotary press), the range of experimental conditions was limited, and could not sufficiently evaluate the reproducibility of results and the robustness of formulations at actual production scale.

Thus, we thought it was necessary to confirm the robustness of applications across a wide range of experimental conditions in terms of method, scale, and speed of mixing and tableting that closely mimicked actual production conditions.

Ceolus™ UF grades were used in this study. Since Ceolus™ UF are MCC grades that have a superior balance of flowability and compactibility with respect to Ceolus™ PH and KG grades, it is anticipated that Ceolus™ UF grades will be more robust to variations in manufacturing process parameters.

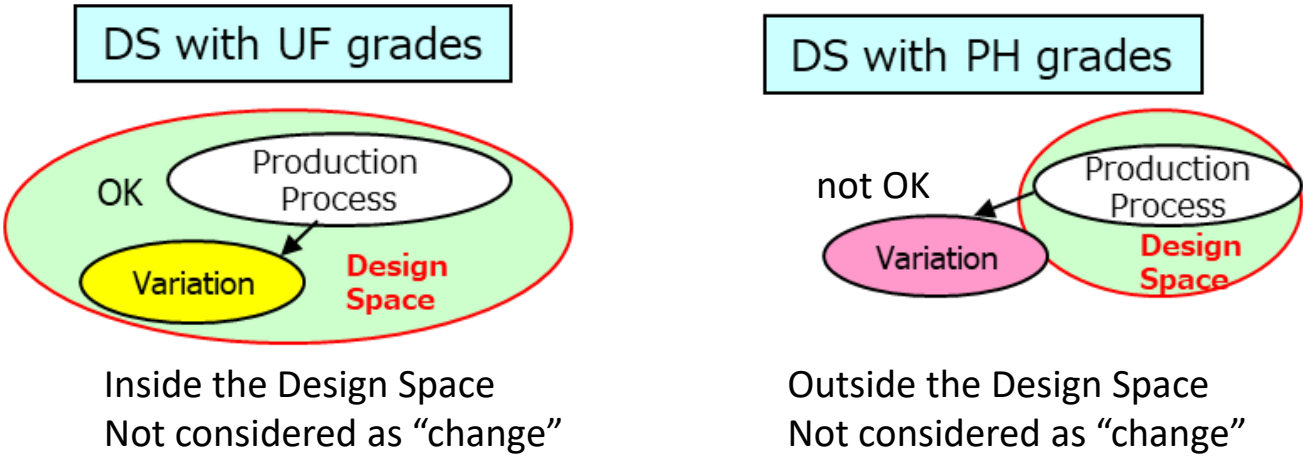


Figure 1. DS using UF and PH Grades of Ceolus™

The aims of this study are to clarify the DS for the use of PH and UF grades of Ceolus™ and confirm whether UF grades are superior to PH grades.

As a step toward DS construction, we chose high API dosage and direct compression for the formulation, both of which are possible using UF grades. In the formulations of UF-711/ascorbic acid and UF-702/acetaminophen, we focused on tablet hardness and tablet weight relative standard deviation (RSD), and selected three important parameters: (1) API dosage, (2) lubricant content, and (3) tableting speed. We then compared the applicable range of the parameters satisfying tablet hardness and tablet weight RSD above a certain level between UF grade and PH grade (PH-102).

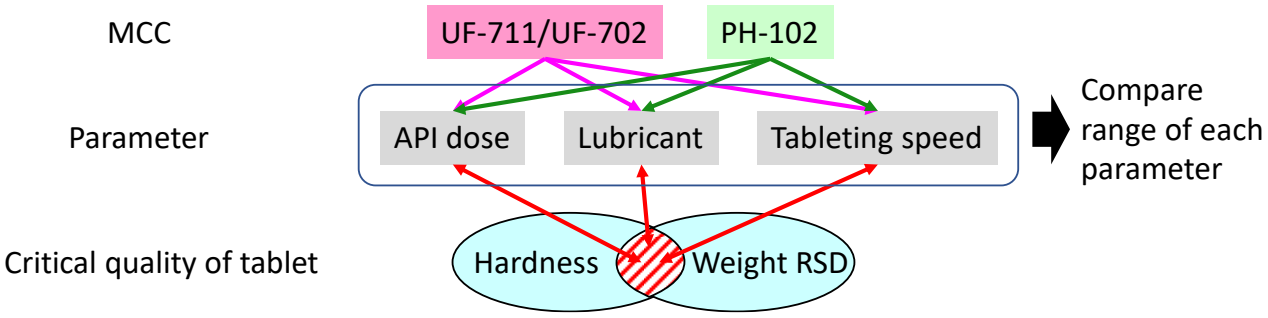


Figure 2. Overview of DS

3. Experiments

Since UF grades enable the development of formulations with high API dosage and the miniaturization of tablets, the use of UF grades is expected to improve drug administration and cost efficiency. Accordingly, in the present study, we selected formulation examples using UF grades and implemented design spacing. Two formulations of UF grades are described below.[2)]

3-1. Direct compression of high-dose ascorbic acid (VC), a low compactible API, using UF-711

1) Experimental procedures

The process for direct compression of high-dose VC, a low compactible API, is shown below.

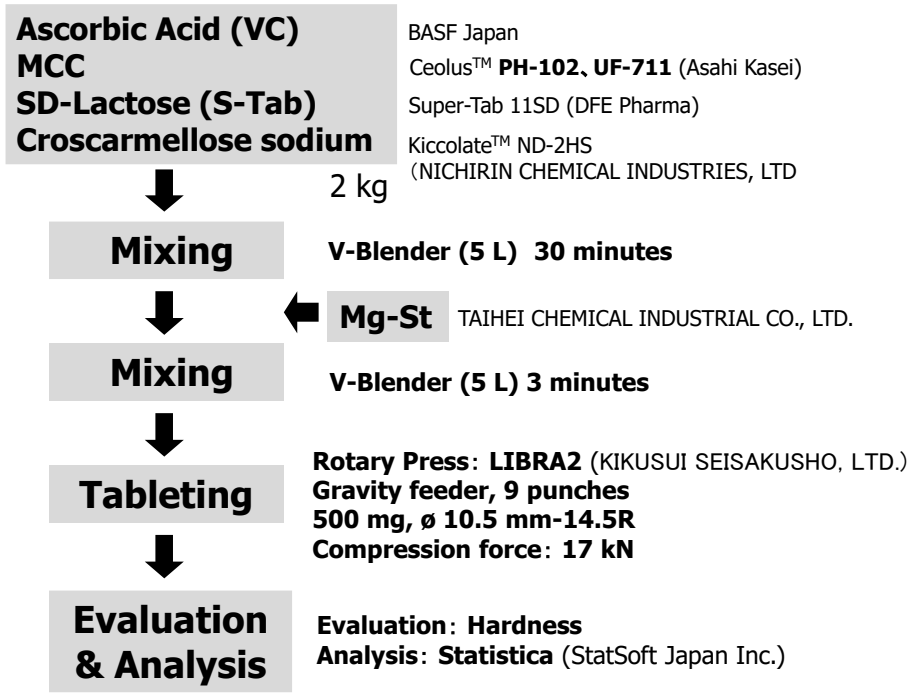


Figure 3. Experimental Flow

Conditions of variation (PP) are shown below.

Formulation					Lubricant		Tableting Conditions
UF-711 (%)	CCS (%)	S-tab (%)	VC content (%)	×	Mg-St content (%)	×	Tableting speed (rpm)
33	2	5	60	×	0.75	×	30
		10	55		1.50		40
		15	50		2.25		50

Formulation					Lubricant		Tableting Conditions
PH-102 (%)	CCS (%)	S-tab (%)	VC content (%)	×	Mg-St content (%)	×	Tableting speed (rpm)
40	2	18	40	×	0.75	×	30
		23	35		1.50		40
		28	30		2.25		50

Figure 4. Conditions of variation

*1 The MCC addition rate was selected based on our previous studies and the results of a

preliminary test.

*2 With an upper VC limit of 60% for the UF formulation and 40% for the PH formulation, the SD-Lactose (S-tab) amount was varied in accordance with the VC content.

*3 Three different conditions for VC content, Magnesium stearate (Mg-St) content, and tableting speed (3 × 3 × 3) were selected for each UF and PH formulation, for a total of 54 conditions.

*4 The target tablet hardness was ≥110 N (approx. 50 N equivalent of ϕ8 mm 180 mg tablet).

2) Experimental results

Tablet hardness results are shown in Table 1, and contribution ratio results of each PP to hardness are shown in Table 2.

Table 1. Tablet hardness results

UF-711 Formulation												
Process Variables			CQA	Process Variables			CQA	Process Variables			CQA
VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)
60	0.75	30	136	55	0.75	30	151	50	0.75	30	187
60	0.75	40	134	55	0.75	40	166	50	0.75	40	192
60	0.75	50	134	55	0.75	50	159	50	0.75	50	185
60	1.5	30	118	55	1.5	30	114	50	1.5	30	144
60	1.5	40	116	55	1.5	40	118	50	1.5	40	147
60	1.5	50	105	55	1.5	50	111	50	1.5	50	138
60	2.25	30	84	55	2.25	30	107	50	2.25	30	142
60	2.25	40	81	55	2.25	40	98	50	2.25	40	139
60	2.25	50	81	55	2.25	50	101	50	2.25	50	137

PH-102 Formulation											
Process Variables			CQA	Process Variables			CQA	Process Variables			CQA
VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	VC (%)	Mg-St (%)	Speed (rpm)	Hardness (N)
40	0.75	30	151	35	0.75	30	135	30	0.75	30	169
40	0.75	40	147	35	0.75	40	133	30	0.75	40	173
40	0.75	50	139	35	0.75	50	134	30	0.75	50	170
40	1.5	30	120	35	1.5	30	123	30	1.5	30	136
40	1.5	40	113	35	1.5	40	118	30	1.5	40	136
40	1.5	50	113	35	1.5	50	114	30	1.5	50	133
40	2.25	30	105	35	2.25	30	102	30	2.25	30	111
40	2.25	40	103	35	2.25	40	101	30	2.25	40	108
40	2.25	50	103	35	2.25	50	99	30	2.25	50	103

*Gray cells represent tablet hardness <110 N as a CQA.

Table 2. Contribution of individual PP to hardness

UF-711 Formulation	
Process Variables	Contribution ratio (%)
VC content	**41.9**
Mg-St content	**53.5**
Tableting speed	0.4

PH-102 Formulation	
Process Variables	Contribution ratio (%)
VC content	15.9
Mg-St content	**76.1**
Tableting speed	1.0

UF-711 formulation: Both Mg-St content and VC content contribute to tablet hardness. Higher drug loading in the formulation (i.e., less lactose) contributes to the compactibility of the tablet.

PH-102 formulation: The contribution from added Mg-St is dominant. The contribution from tableting speed is small.

UF-711 formulation: Both Mg-St content and VC content affected the hardness, and higher hardness was achieved using lower amounts of Mg-St and VC".

PH-102 formulation: Mg-St content strongly affected the hardness, particularly in areas with high Mg-St content. Hardness did not increase when drug loading was reduced.

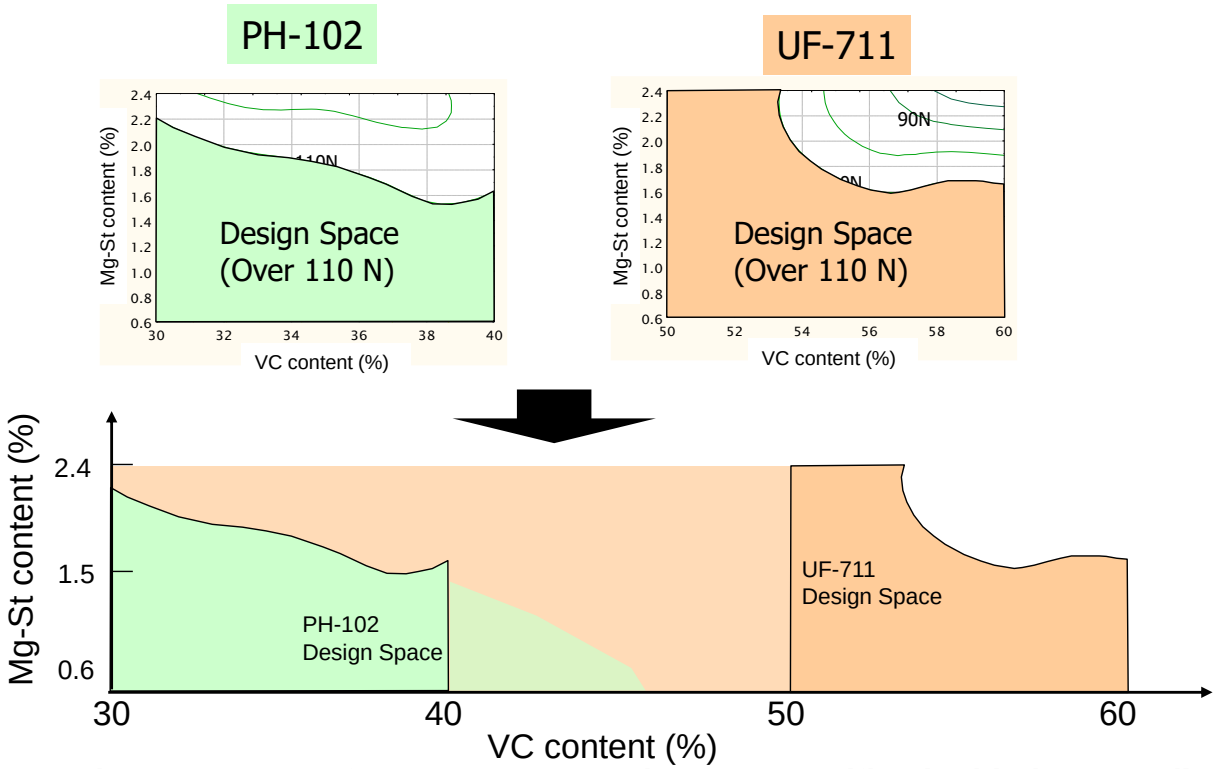


Figure 5. Effect of Mg-St content and VC content (fixed tableting speed)

UF-711 was able to contain 20% more VC than PH-102, and the coverage was equal or higher in hardness.

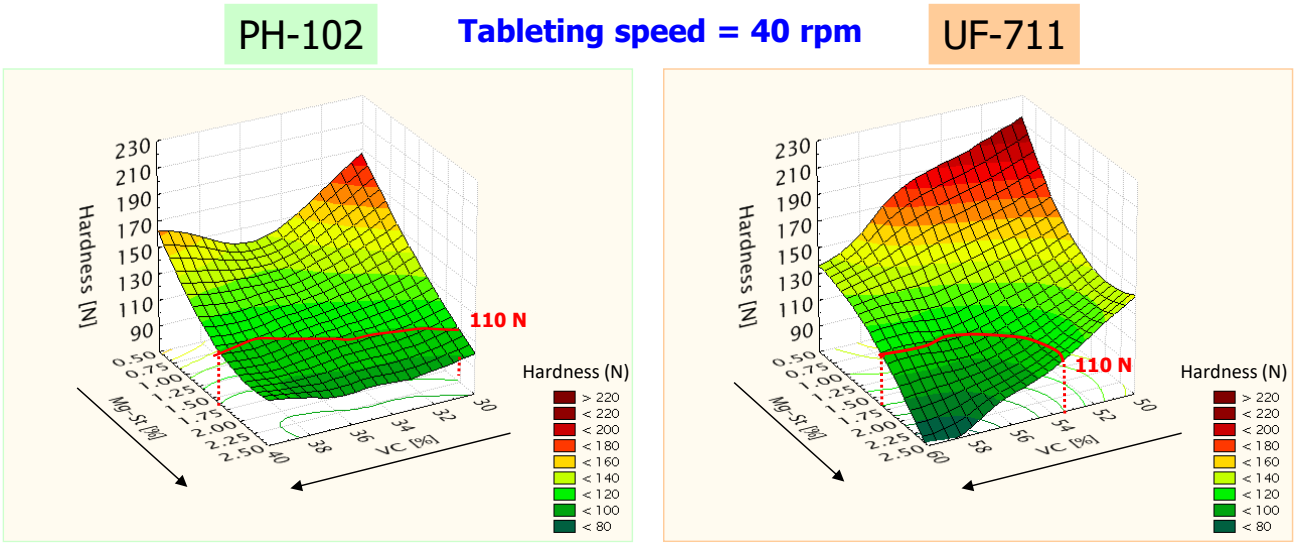


Figure 6. Coverage comparison

PH-102/VC・30% exhibited decreased hardness in areas with high Mg-St content, but UF-711/VC・50% maintained higher hardness even at high Mg-St content. These results indicate that use of UF-711 would reduce tableting issues.

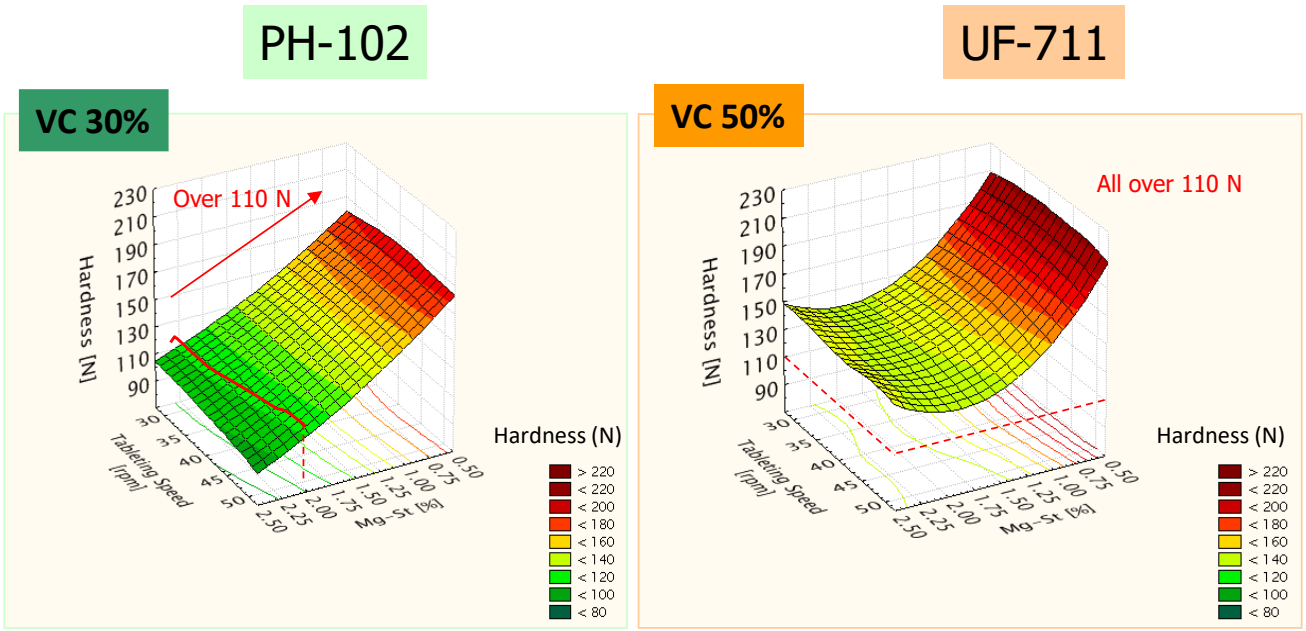


Figure 7. Effect of Mg-St (fixed VC content)

The results of direct compression within the DS using the high-dose UF-711/ascorbic acid, VC, low compactible API are summarized below.
Comparisons of UF-711 and PH-102 with regard to the applicable range of the API content, Mg-St content, and tableting speed for a target tablet hardness ≥110 N revealed the following:

1) In the UF-711 formulation, even if the VC content was >20% compared to the PH-102 formulation, the hardness was equal or higher.
2) In the UF-711 formulation, the applicability of API content, Mg-St content, and tableting speed was comparable or better than that for the PH-102 formulation.
3) The tablet hardness was higher in the UF-711/VC・50% formulation, and the decrease in the hardness was also less at a high added Mg-St content of 2.25%. These findings imply that the use of UF-711 would prevent tableting issues (minimal impact on hardness at high Mg-St content), and UF-711 is expected to be highly robust against variations in other factors (e.g., low compactibility due to altered physical properties of the API).

3-2. Direct compression of acetaminophen (APAP), a low compactible and low flowable API, using UF-702

The process for direct compression of APAP, a low compactible and low flowable API, is shown below.

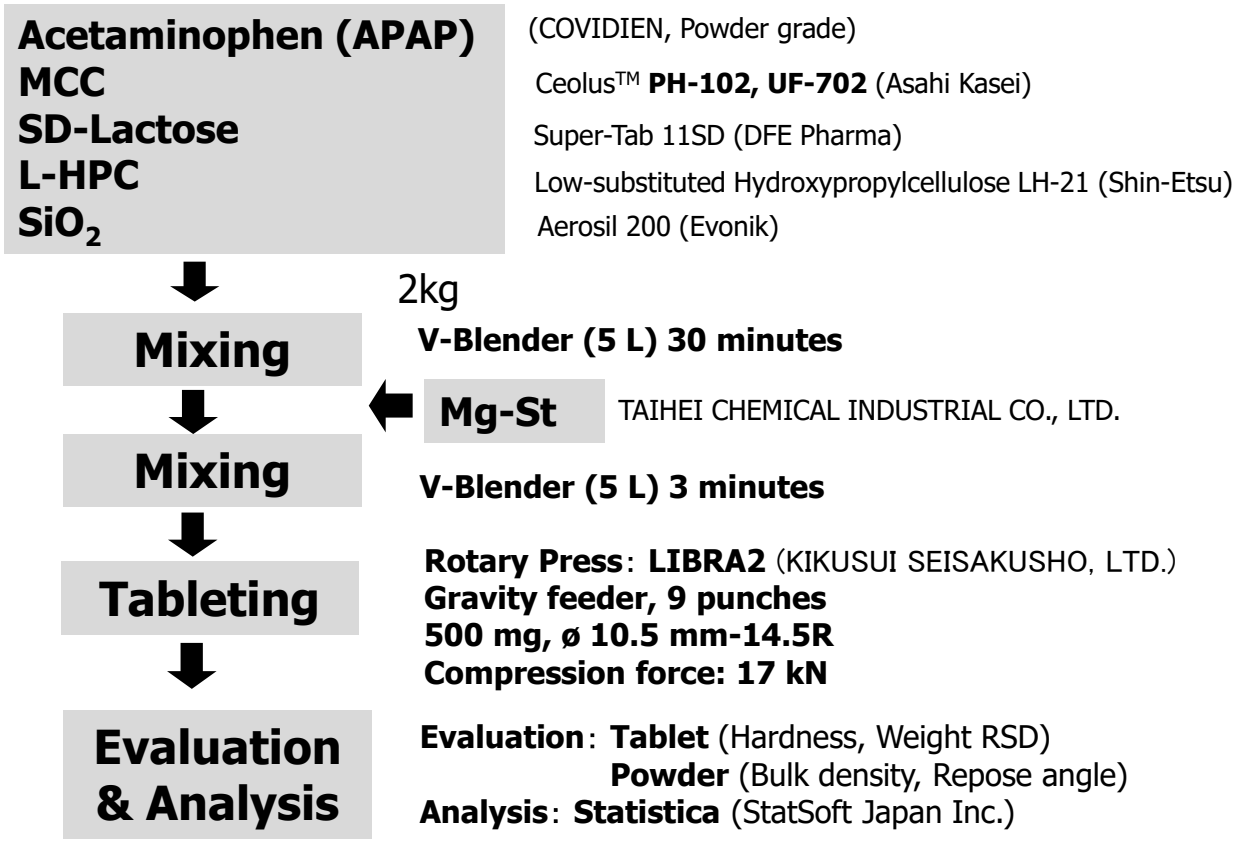


Figure 8. Experimental Procedure

Conditions of variation (PP) are shown below.

Formulation						Lubricant		Tableting Conditions
UF-702 (%)	L-HPC (%)	S-tab (%)	SiO_2 (%)	APAP content (%)	×	Mg-St content (%)	×	Tableting speed (rpm)
30	5	20	0.675	45		0.75		30
		25	0.600	40		1.00		40
		30	0.525	35		1.50		50
		35	0.450	30		2.25		

Formulation						Lubricant		Tableting Conditions
PH-102 (%)	L-HPC (%)	S-tab (%)	SiO_2 (%)	APAP content (%)	×	Mg-St content (%)	×	Tableting speed (rpm)
30	5	25	0.600	40		0.75		30
		30	0.525	35		1.00		40
		35	0.450	30		1.50		50
						2.25		

Figure 9. Conditions of variation

2) Experimental results

Tablet hardness results are shown in Table 3, and contribution ratio results of each PP to hardness are shown in Table 4.

Table 3. Tablet hardness and tablet weight RSD results

UF-702 Formulation

Process Variables			CQA		Process Variables			CQA		Process Variables			CQA		Process Variables			CQA	
APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)	APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)	APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)	APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)
45	0.75	30	123	0.50	40	0.75	30	134	0.39	35	0.75	30	139	0.34	30	0.75	30	157	0.21
45	0.75	40	121	0.47	40	0.75	40	132	0.32	35	0.75	40	139	0.36	30	0.75	40	148	0.40
45	0.75	50	116	0.94	40	0.75	50	127	0.54	35	0.75	50	134	0.35	30	0.75	50	142	0.65
45	1.00	30	106	0.43	40	1.00	30	112	0.51	35	1.00	30	124	0.27	30	1.00	30	133	0.30
45	1.00	40	100	0.35	40	1.00	40	107	0.51	35	1.00	40	119	0.37	30	1.00	40	131	0.31
45	1.00	50	98	0.54	40	1.00	50	107	0.39	35	1.00	50	118	0.51	30	1.00	50	141	0.34
45	1.50	30	94	0.68	40	1.50	30	91	0.24	35	1.50	30	109	0.44	30	1.50	30	113	0.38
45	1.50	40	88	0.38	40	1.50	40	89	0.51	35	1.50	40	108	0.48	30	1.50	40	119	0.36
45	1.50	50	89	0.83	40	1.50	50	97	0.56	35	1.50	50	106	0.39	30	1.50	50	112	0.54
45	2.25	30	81	0.37	40	2.25	30	88	0.72	35	2.25	30	93	0.51	30	2.25	30	114	0.32
45	2.25	40	78	0.68	40	2.25	40	81	0.55	35	2.25	40	88	0.45	30	2.25	40	98	0.53
45	2.25	50	76	1.87	40	2.25	50	78	0.57	35	2.25	50	83	0.73	30	2.25	50	98	0.67

PH-102 Formulation

Process Variables			CQA		Process Variables			CQA		Process Variables			CQA	
APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)	APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)	APAP (%)	Mg-St (%)	Speed (rpm)	Hardness (N)	Weight RSD (%)
40	0.75	30	128	0.66	35	0.75	30	139	0.27	30	0.75	30	141	0.36
40	0.75	40	124	0.36	35	0.75	40	128	0.47	30	0.75	40	138	0.36
40	0.75	50	120	1.03	35	0.75	50	126	0.51	30	0.75	50	127	0.37
40	1.00	30	94	0.39	35	1.00	30	112	0.33	30	1.00	30	136	0.41
40	1.00	40	96	0.47	35	1.00	40	106	0.46	30	1.00	40	120	0.49
40	1.00	50	97	1.20	35	1.00	50	101	0.60	30	1.00	50	115	0.32
40	1.50	30	94	1.00	35	1.50	30	108	0.35	30	1.50	30	114	0.50
40	1.50	40	96	1.01	35	1.50	40	102	0.47	30	1.50	40	119	0.33
40	1.50	50	61	3.76	35	1.50	50	102	0.46	30	1.50	50	108	0.39
40	2.25	30	84	0.39	35	2.25	30	90	0.37	30	2.25	30	105	0.35
40	2.25	40	78	0.47	35	2.25	40	84	0.38	30	2.25	40	93	0.69
40	2.25	50	72	3.00	35	2.25	50	81	1.40	30	2.25	50	95	1.25

*Gray cells represent tablet hardness <110 N and/or tablet weight RSD >1% as CQA.

Table 4. Contribution of individual PP to tablet hardness and tablet weight RSD

UF-702 Formulation		
Process Variables	Contribution ratio (%)	
	Hardness	Weight RSD
APAP content	26.4	26.0
Mg-St content	71.2	24.6
Tableting speed	2.1	43.2

PH-102 Formulation		
Process Variables	Contribution ratio (%)	
	Hardness	Weight RSD
APAP content	30.3	36.6
Mg-St content	60.2	11.4
Tableting speed	8.6	44.9

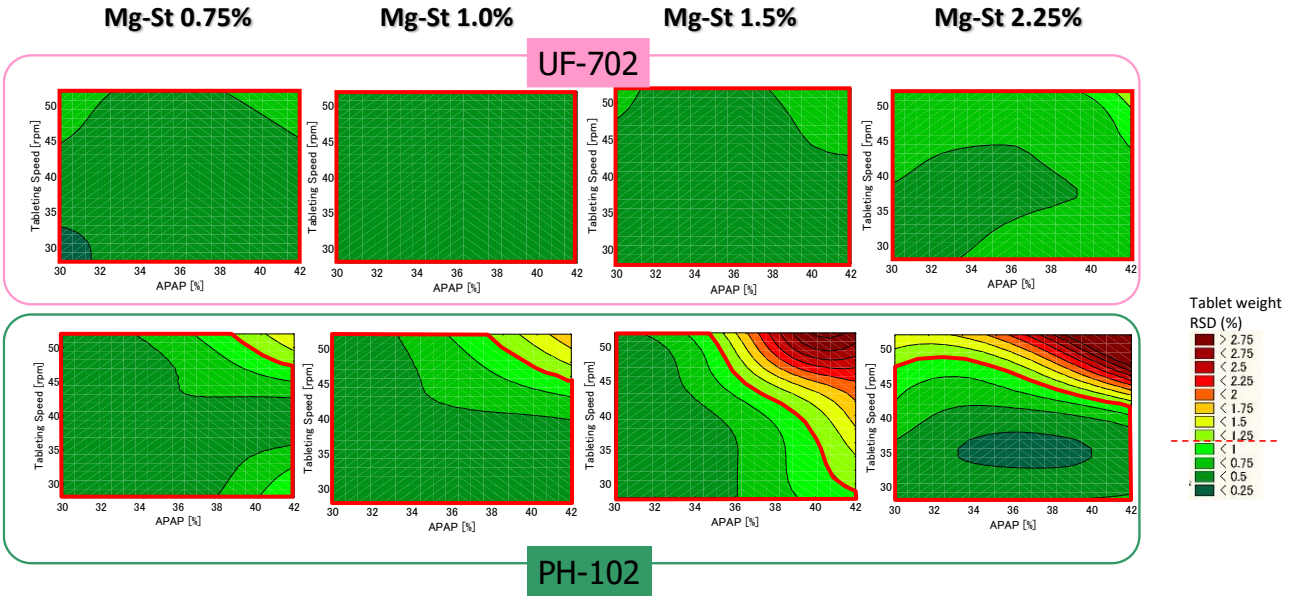


Figure 10. Tablet weight RSD (fixed Mg-St content)

UF-702 formulation: Tablet weight RSD is stable regardless of the Mg-St content. The applicable range of UF-702 is wide.

PH-102 formulation: Tablet weight RSD increased as tableting speed and API content increased.

As the Mg-St content increased, tablet weight RSD increased even at low API content.

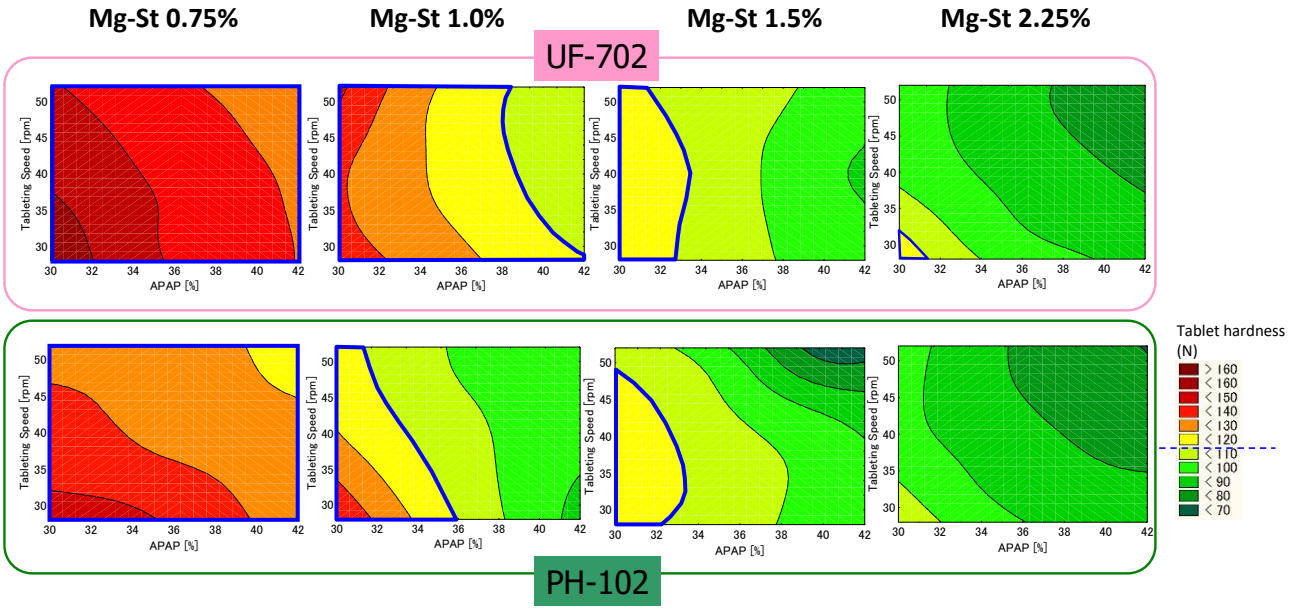


Figure 11. Hardness (fixed Mg-St content)

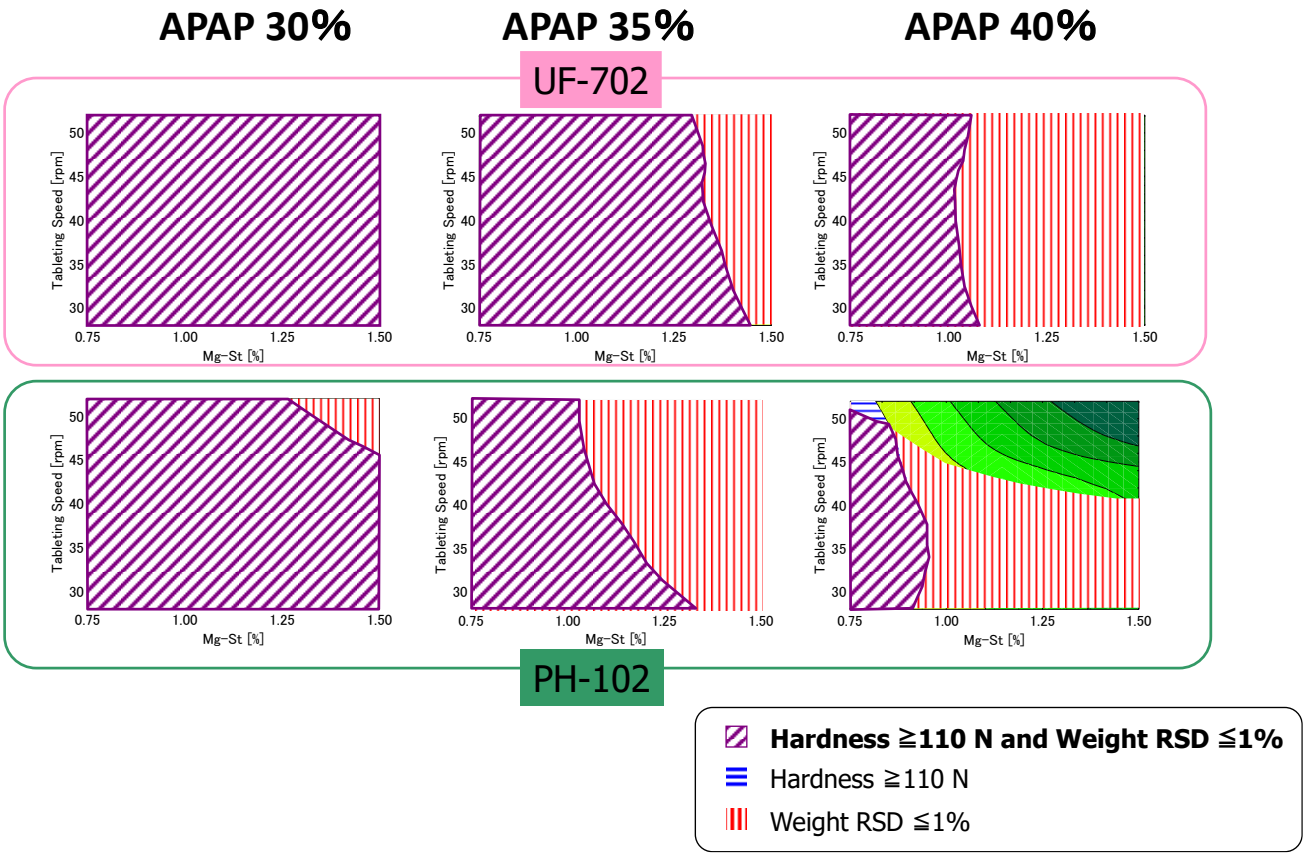


Figure 12. Tablet weight RSD and hardness (fixed APAP content)

UF-702 formulation: Mg-St applicable range was wider when APAP content was high.
PH-102 formulation: Mg-St applicable range was narrow, and tablet hardness decreased as the tableting speed increased.
These findings indicate that UF-702 has a wide range of applications.

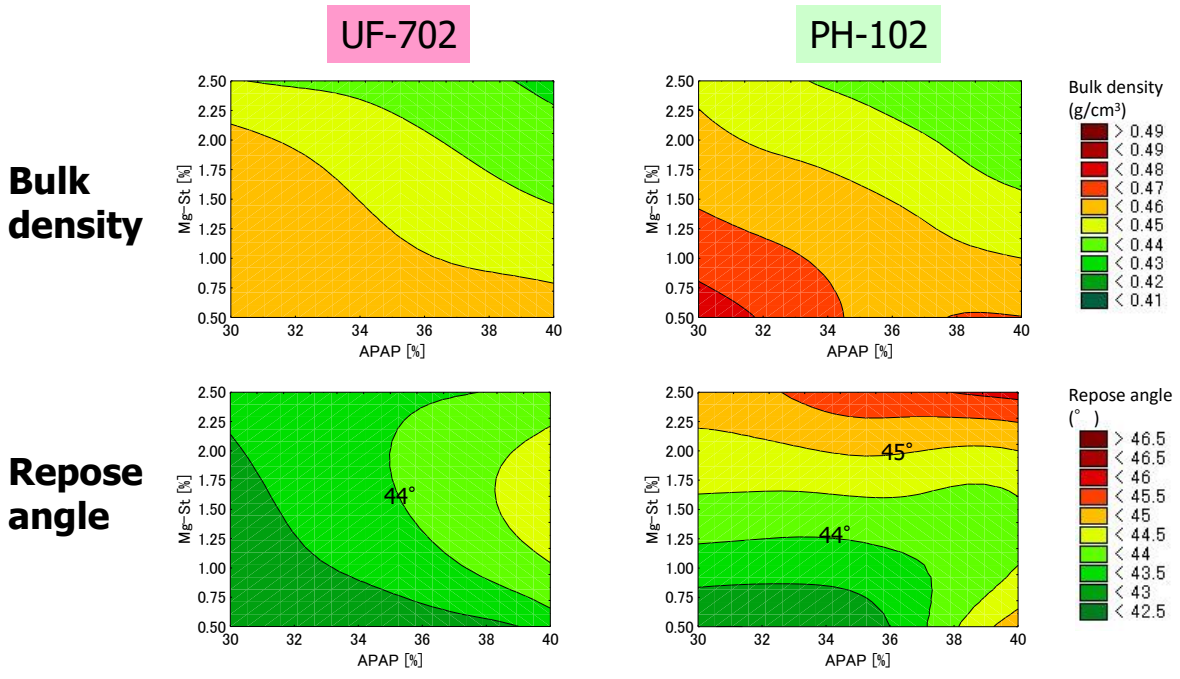


Figure 13. Powder properties

PH-102 formulation: Both bulk density and angle of repose were significantly affected by Mg-St content.
UF-702 formulation: This formulation was less affected by Mg-St content and showed smaller changes in bulk density and angle of repose.

4. Summary

The results of direct tableting of UF-702/APAP, a low compactible and low flowable API, are summarized below.

Comparisons of UF-702 and PH-102 with regard to the applicable range of the API content, Mg-St content, and tableting speed for a target tablet hardness ≥110 N and tablet weight RSD ≤1% revealed the following:

1）The UF-702 formulation showed a wide applicable range of hardness, API content, tablet weight RSD, Mg-St content, and tableting speed compared to the PH-102 formulation.
2）The bulk density and angle of repose of the UF-702 formulation was less affected by variations in the Mg-St content.
3）It was possible to increase the API content, because the decrease in tablet hardness was not caused by low Mg-St content compared to the PH-102 formulation.
4）When the API content is maintained, the variations in hardness and tablet weight RSD of the UF-702 formulation due to the increase in tableting speed and Mg-St content are small compared to those of the PH-102 formulation. Therefore, use of the UF-702 formulation mitigates tableting issues and enables increases in tableting speed. Thus, various benefits can be expected from the UF-702 formulation, such as shortening the formulation development time, reducing production costs, ensuring robustness in terms of compactibility or flowability of the API and also against variations in other factors.

5. Conclusions

As a step toward building a DS for direct compression using MCCs, we compared the applicable PP range between Ceolus™ UF grades and PH-102 in the following formulations:

3-1. Direct compression of VC, a low compactible API, using UF-711
3-2. Direct compression of APAP, a low compactible and low flowable API, using UF-702

Ceolus™ UF grades showed a wider coverage for these PP than PH-102, when varying API content, lubricant content, and tableting speed.

The following conclusions can be drawn based on the above results:

- UF grades have a wide applicable range for API content, lubricant content, and tableting speed.
- UF grades also have wide coverage for other factors.
- Use of UF grades facilitates robust formulation design at the formulation development stage.

References

1) Forum proceedings for the 1st to 3rd study forum for standardized formulation
2) Obae *et al.*, Ceolus report Vol.6, p.26-33(2008)