Characteristics of Microcrystalline Cellulose Grades Suitable for Continuous Direct Compression System

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EXECUTIVE SUMMARY

・The continuous production system, especially the continuous direct compression process (CDC) is attracting attention as it doesn't need the scale-up process of development thus can reduce the production cost.

・In this study, we compared different types of MCC grades called CEOLUS™ (Table 1.) to investigate what powder properties contribute to process compatibility and which grade is suitable for CDC system.

・As the result, we found Basic Flow Energy (BFE) as an important parameter for powder mixing uniformity.

・ Among the samples tested, KG-1000 had the lowest BFE, excellent content uniformity due to the uniform progress of powder mixing, and other excellent tablet properties.

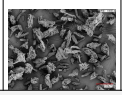
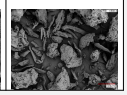
	KG-1000	KG-802	UF711	PH-102
Particle size D50 (μm)	50	50	50	90
Bulk density (g/mL)	0.12	0.21	0.22	0.30
Repose angle (°)	57	49	42	42
SEM Image (×500)				

Table 1. Powder properties of MCCs

EXPERIMENT METHODS

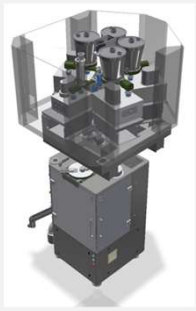
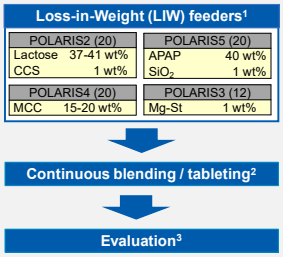


Figure 2. Image of CDC system (CRA-RIS SYSTEM)

No.	1	2	3	4
Formulation	KG-1000[1]	KG-802	UF-711	PH-102
Acetaminophen (APAP)	40	40	40	40
Spray-dried lactose (Lactose)	41	37	37	37
MCC:CEOLUS™	15	20	20	20
Croscarmellose sodium (CCS)	2	1	1	1
Silicon dioxide (SiO_2)	1	1	1	1
Magnesium stearate (Mg-St)	1	1	1	1
Bulk density (g/mL)	0.416	0.433	0.440	0.470
Repose angle (°)	46	43	42	42

Table 2. Formulation and properties of powder mix



1: Due to the limited number of LIW feeders, lactose and CCS, APAP and SiO_2 are premixed and set in the LIW feeder.

2: Continuous direct compression system: CRA-RIS SYSTEM (Kikusui Seisakusho)
45 punches, Turntable rotation speed: 41.2 rpm
Force feeder rotation speed: 45 rpm
CRATER screen diameter: φ3.0 mm (KG-1000)
φ2.0 mm (KG-802, UF-711, PH-102)
Tablet size: 180 mg, φ8 mm - 12R
Run time: 60 min
Sampling time: 0, 2, 4, 6, 8, 10, 15, 30, 45, 60 min
Compression Force: (Main compression) 12 kN
(Pre-compression) 6 kN

3: Tablet weight, API content, tablet hardness, friability, disintegration and dissolution

Figure 1. Procedure of continuous direct compression production

RESULTS AND DISCUSSIONS

Feed Rate of MCCs from Loss-in-Weight feeder

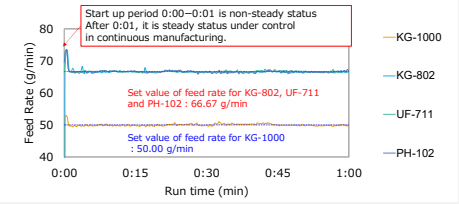


Figure 3. feed rate of each CEOLUS™ grades during the run time

Table 3. feed rate of each CEOLUS™ grades

	KG-1000	KG-802	UF-711	PH-102
Set value of feed rate (g/min)	50.00	66.67	66.67	66.67
Actual feed rate (g/min)	49.98	66.53	66.62	66.58
σ	0.27	0.22	0.23	0.23

- All CEOLUS™ grades showed constant feed rate from loss-in-weight feeder under steady status.

Tablet Weight RSD

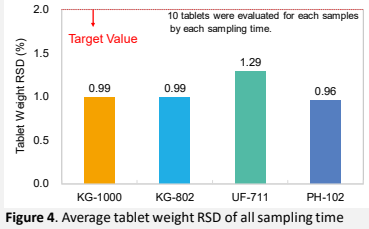


Figure 4. Average tablet weight RSD of all sampling time

- All formulations were within the target value of tablet weight RSD.

API content RSD

$$RSD = \frac{\text{Standard deviation}}{\text{Mean}} \times 100\ (\%)$$

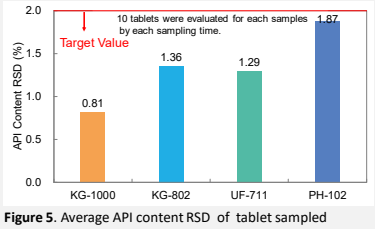


Figure 5. Average API content RSD of tablet sampled at 0, 15, 30, 45 and 60 minute.

・KG-1000 showed the lowest API content RSD.

Tablet Hardness

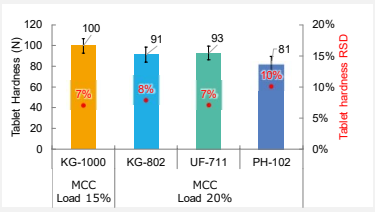


Figure 8. Average hardness of tablets of all sampling time

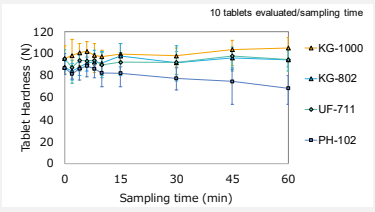


Figure 9. Tablet hardness at each sampling time

- KG-1000 showed highest tablet hardness and lowest hardness RSD.

Dynamic flowability of CEOLUS™ grades measured by powder rheometer

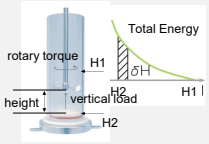


Figure 6. Picture of powder rheometer FT-4 and image of measurement principle

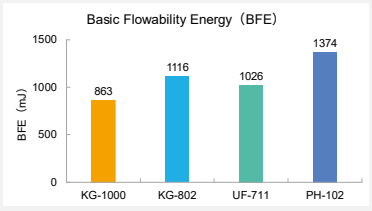


Figure 7. Basic Flowability Energy of CEOLUS™

- KG-1000 showed the lowest BFE energy per volume among all CEOLUS™ grades.
- It is considered that powder mixing proceeds uniformly with small BFE.

Friability of Tablets

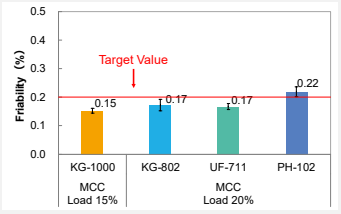


Figure 10. Average friability of all sampling time

- KG-1000, KG-802 and UF-711 were within target value of friability .

Disintegration Time of Tablets

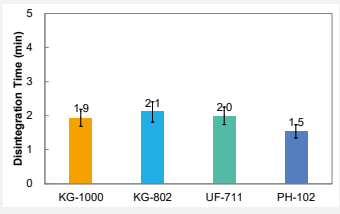


Figure 11. Average disintegration time of all sampling time

- All formulations showed favorable disintegration time (less than 3min).

Dissolution profile of Tablets

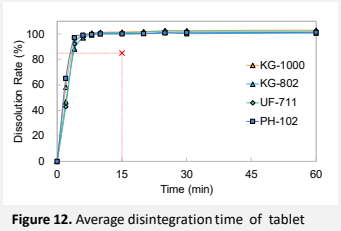


Figure 12. Average disintegration time of tablet sampled at 0, 15, 30, 45 and 60 minute.

- All formulations showed favorable dissolution profiles (higher than 85% at 15 minutes).

Tablet properties

Table 4. Summary of tablet evaluation results

No.		1	2	3	4
Items	Target	KG-1000	KG-802	UF-711	PH-102
Tablet Weight RSD	<2.0%	1.0%	1.0%	1.3%	1.0%
API content RSD	<2.0%	0.81%	1.36%	1.29%	1.87%
Tablet Hardness	>50N	100 N	91 N	93 N	81 N
Tablet Hardness RSD	-	7%	8%	7%	10%
Friability	<0.20%	0.15%	0.17%	0.17%	0.22%
Disintegrating Time	<30 min	1.9 min	2.1 min	2.0 min	1.5 min
Dissolution rate After 15 min	>85%	100%	100%	100%	99.7%

- CEOLUS™ KG-1000 showed the best performance among all CEOLUS™ grades.

ACKNOWLEDGMENT

We would like to thank everyone at KIKUSUI SEISAKUSHO LTD for allowing us to use the continuous production system equipment in conducting this research.