# Comparison of Ceolus™ Grades in Continuous Manufacturing of Tablets using Direct Compression

Asahi Kasei Corporation
CEOLUS R&D Department
Akihiro Azetsu

## 1. Introduction

The introduction of continuous manufacturing of tablets has been gaining momentum, because it offers reductions in development and manufacturing costs and time and improved reliability of quality assurance. In this study, grades of Ceolus™, microcrystalline cellulose (MCC) in formulations containing 40% fine powder-type drug, were compared using the CRA-RIS SYSTEM (Figs. 1, 2), a direct compression, continuous manufacturing system produced by Kikusui Seisakusho Ltd. The feasibility of stable continuous manufacturing and the MCC grades that could produce tablets with the best physical properties were investigated.

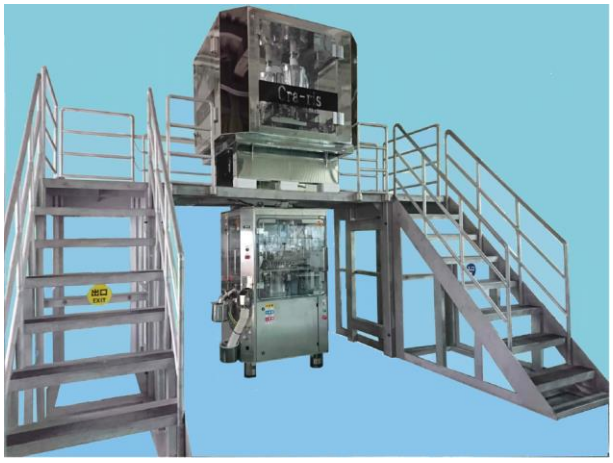


Fig. 1. CRA-RIS SYSTEM (Kikusui Seisakusho Ltd.)


Fig. 2 External view of CRA-RIS SYSTEM

Provided by Kikusui Seisakusho Ltd.

## 2. Experiment

### 2-1. Materials

API: Acetaminophen (APAP) fine powder

Excipients: MCC, Ceolus™ KG-1000, KG-802, UF-711, PH-102, Asahi Kasei Corporation

Excipients: Spray dried lactose (SD lactose)

Disintegrant: Croscarmellose Sodium (CCS), Kiccolate™ ND-2HS, Nichirin Chemical Industries, Ltd.

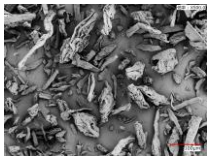
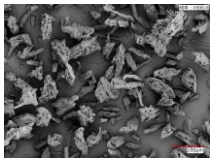
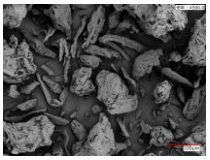
Fluidizer: Fine silicon dioxide ($SiO_2$)

Lubricant: Magnesium stearate (Mg-St)

Table 1 shows the powder properties of the Ceolus™ grades, Table 2 shows the powder properties of APAP, and Table 3 shows the test formulations and blend powder properties.

The Ceolus™ grades selected for the study were direct compression standard grade PH-102, and the high compactable grades KG-1000, KG-802, and UF-711.

Table 1 Powder properties of the Ceolus™ grades

| Grade | KG-1000 | KG-802 | UF-711 | PH-102 |
|---|---|---|---|---|
| Particle diameter D50 (μm) | 50 | 50 | 50 | 90 |
| Bulk density (g/mL) | 0.12 | 0.21 | 0.22 | 0.30 |
| Angle of repose (°) | 57 | 49 | 42 | 42 |
| SEM image (×500) |  |  |  |  |

Note: All values are presented only for the purpose of basic reference and not as specifications.

Table 2 Powder properties of APAP

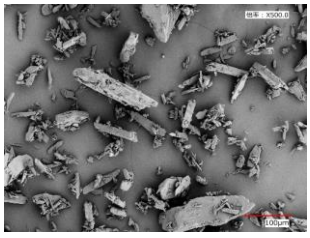
| | |
|---|---|
| Particle diameter D50 (μm) | 36 |
| Bulk density (g/mL) | 0.19 |
| Angle of repose (°) | 53 |
| SEM image (×500) |  |

Table 3 Test formulations and blend powder properties

| No. | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| MCC | | KG-1000 [1] | KG-802 | UF-711 | PH-102 |
| Formulation (wt%) | APAP | 40 | 40 | 40 | 40 |
| | SD lactose | 41 | 37 | 37 | 37 |
| | MCC | 15 | 20 | 20 | 20 |
| | CCS | 2 | 1 | 1 | 1 |
| | $SiO_2$ | 1 | 1 | 1 | 1 |
| | Mg-St | 1 | 1 | 1 | 1 |
| Powder properties [2] | Bulk density (g/mL) | 0.42 | 0.43 | 0.44 | 0.47 |
| | Angle of repose (°) | 46 | 43 | 42 | 42 |

[1] KG-1000, which has the highest compactability, achieved good hardness even when added in small amounts, so the added volume was decreased to 5% lower than the other formulations. The added volume of CCS was increased by 1% because slow dissolution was expected.

[2] Powder properties were measured in powder samples taken from the force feeder after the end of the continuous manufacturing test.

**2-2. Procedures for the experiment**

1) Preparation

Trial tableting: Trial tableting was carried out for several minutes with each formulation to produce tablets of the target weight. As a result, the CRATER granulating screen diameter for KG-1000 was adjusted from φ2.0 mm to φ3.0 mm.

2) Continuous manufacturing

Direct compression, continuous manufacturing system: CRA-RIS SYSTEM (Kikusui Seisakusho Ltd.)

Tablet press conditions: 45 punches, turntable rotation speed 41.2 rpm, force feeder rotation speed 45 rpm

CRATER granulating screen diameter: φ3.0 mm (KG-1000), φ2.0 mm (KG-802, UF-711, PH-102)

Tablet weight, diameter: 180 mg, φ8.0 mm–12R

Pressure: 12 kN (main pressure), 6 kN (pre-pressure)

Continuous manufacturing time: 60 min

Sampling time: 0, 2, 4, 6, 8, 10, 15, 30, 45, 60 min (AP content RSD and dissolution evaluated at 0,

15, 30, 45, 60 min)

The experimental procedure is shown in Fig. 3.

| POLARIS 2（20） | |
|---|---|
| Lactose | 37-41 wt% |
| CCS | 1-2 wt% |

| POLARIS 5（20） | |
|---|---|
| APAP | 40 wt% |
| $SiO_2$ | 1 wt% |

| POLARIS 3（12） | |
|---|---|
| Mg-St | 1 wt% |

| POLARIS 4（20） | |
|---|---|
| MCC | 15-20 wt% |








Fig. 3 Experimental procedure for continuous manufacturing

3) Evaluation of properties

Tablet weight RSD (%): Ten tablets were weighed using an electronic balance. Tablet weight RSD (%) was then obtained from the mean and standard deviation (SD) using the following formula.

Tablet weight RSD (%) = SD/mean × 100 (target ≤2%)

API content RSD (%): The content of ten tablets was measured in a dissolution tester (NT-60, JASCO Corporation) using Japanese Pharmacopoeia Solution 1, with paddle rotation speed of 50 rpm. API content RSD (%) was then obtained from the mean and SD using the following formula.

API content RSD (%) = SD/mean × 100 (target ≤2%)

Tablet hardness (N): The hardness of 10 tablets was measured using a hardness meter (Tablet Tester 8M, Dr. Schleuniger). The mean value was used. (target ≥50 N).

Friability (%): This was measured using a friability tester (PTF 30ERA, Pharma Test) with 37 tablets, 25 rpm, for 4 minutes. (target ≤0.20%)

Disintegration time (min): The disintegration time for 6 tablets was measured using a disintegration tester (NT-40HS, Toyama Sangyo Co., Ltd.) with purified water at 37 °C and no disc, and the mean time was used. (target: ≤30 min)

Dissolution test: The change in dissolution rate in 60 minutes was measured using a dissolution tester (NT-60, JASCO Corporation) with Japanese Pharmacopoeia Solution 1 and paddle

rotation speed of 50 rpm.

The dissolution rate was measured in 2 tablets, and the mean value was used.

(target: dissolution rate ≥85% at 15 min from start)

**2-3 Results**

Fig. 4 shows the changes in feed volume from the POLARIS 4 loss-in-weight feeder. Apart from a non-steady state lasting about 1 minute after start-up, it was confirmed that all of the four evaluated grades were supplied in a stable manner in line with the set values.

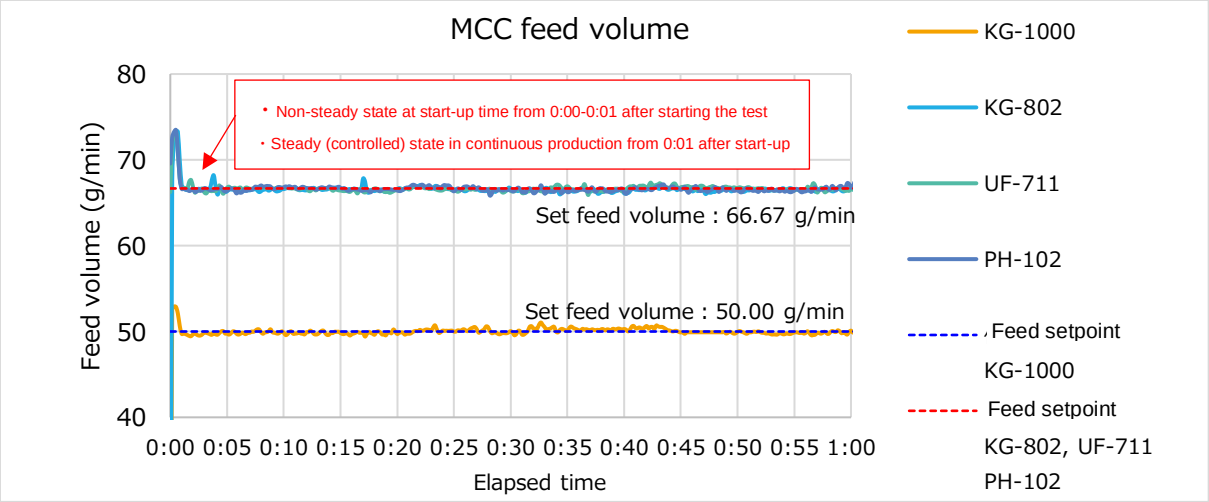



Fig. 4 MCC feed volume data

Fig. 5 shows tablet weight and weight RSD for each formulation at each sampling time, and Fig. 6 shows the mean weight RSD for each formulation at each sampling time. Tablet weight RSD results were good, meeting the target of ≤2% in all formulations.

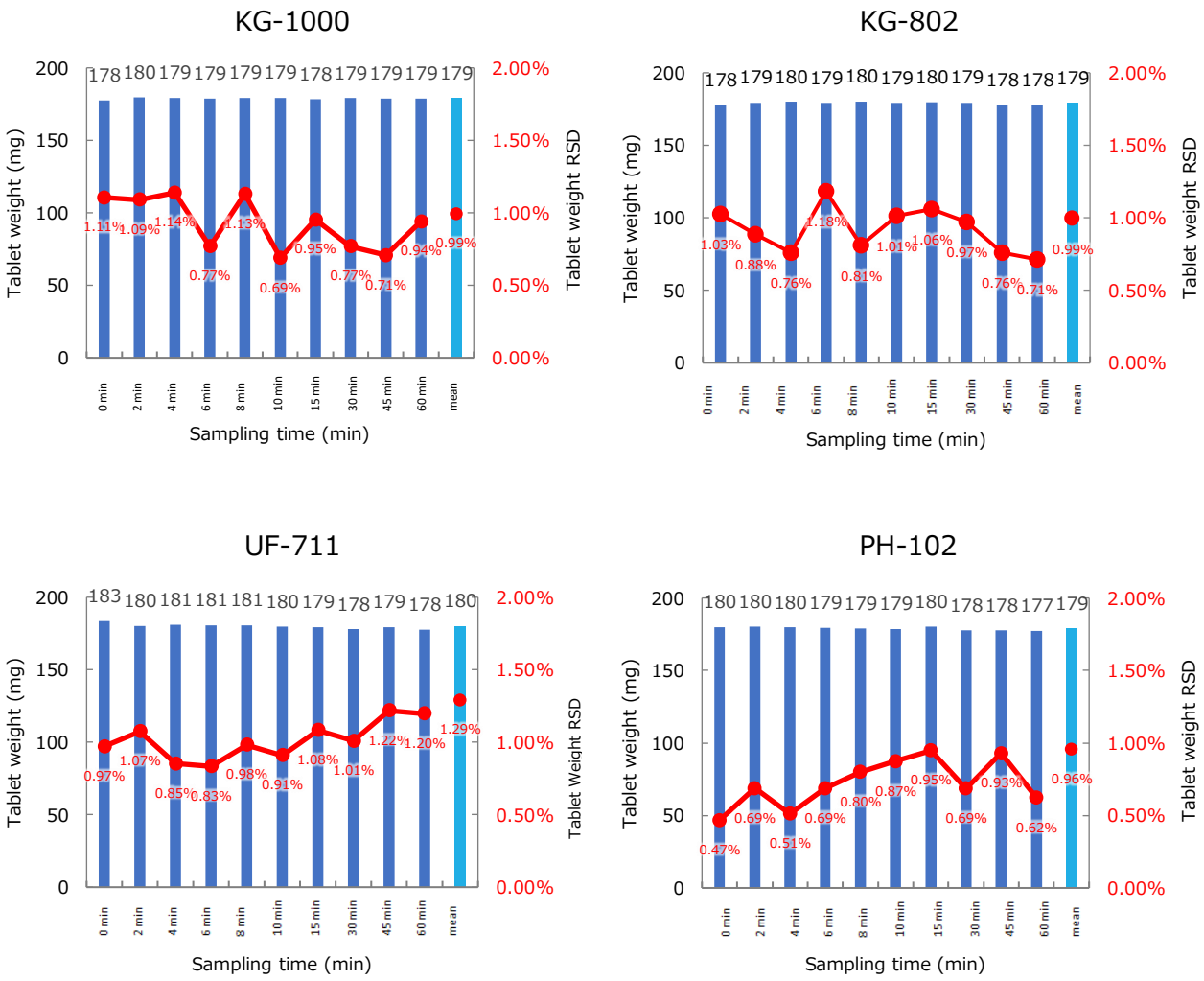



Fig. 5 Mean tablet weight and weight RSD for each formulation at each sampling time

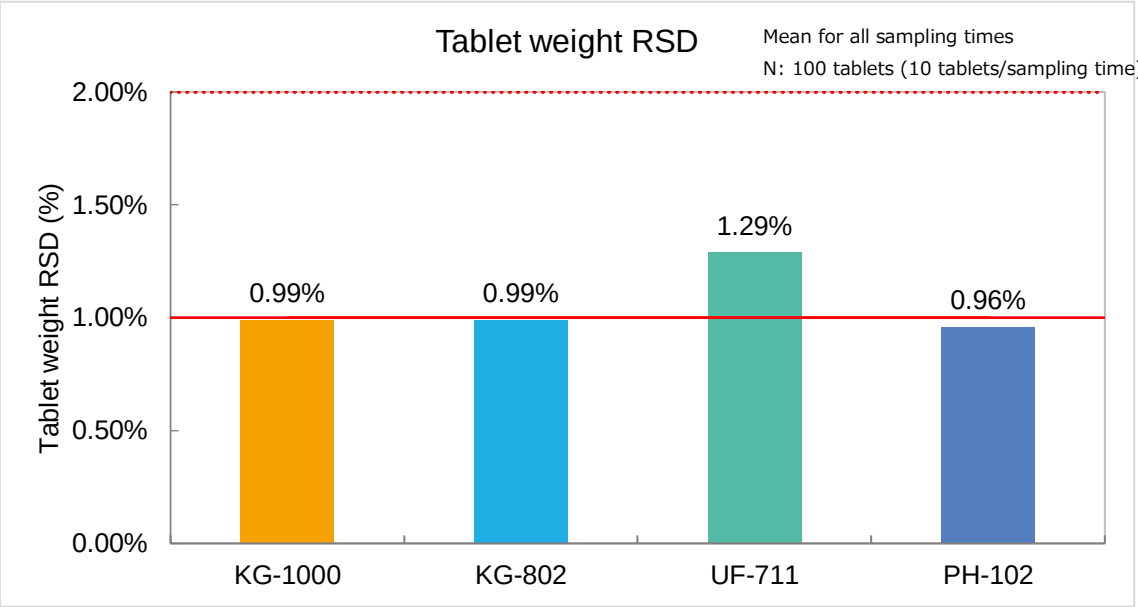



Fig. 6 Mean tablet weight RSD of each formulation

Fig. 7 shows APAP content in the tablet at 0, 15, 30, 45, and 60 minutes and API content RSD, and Fig. 8 shows the mean API content RSD for all sampling times. API content RSD reached the target of ≤2% in all formulations. The result was particularly good for KG-1000, which had the lowest API content RSD.

Figs. 9 and 10 show the basic flowability energy (BFE) for equal volumes of Ceolus™ grades measured with the FT-4 Powder Rheometer.

Of the Ceolus™ grades compared in this study, KG-1000 had the lowest BFE, indicating that it flows with the smallest force per volume for equal volumes. This is presumably because KG-1000 is light and has a long fibrous form. Because of this superior dynamic flowability, it is thought that KG-1000 mixes well with the other powders during the mixing stage in continuous manufacturing, resulting in a lower API content RSD than the other grades.

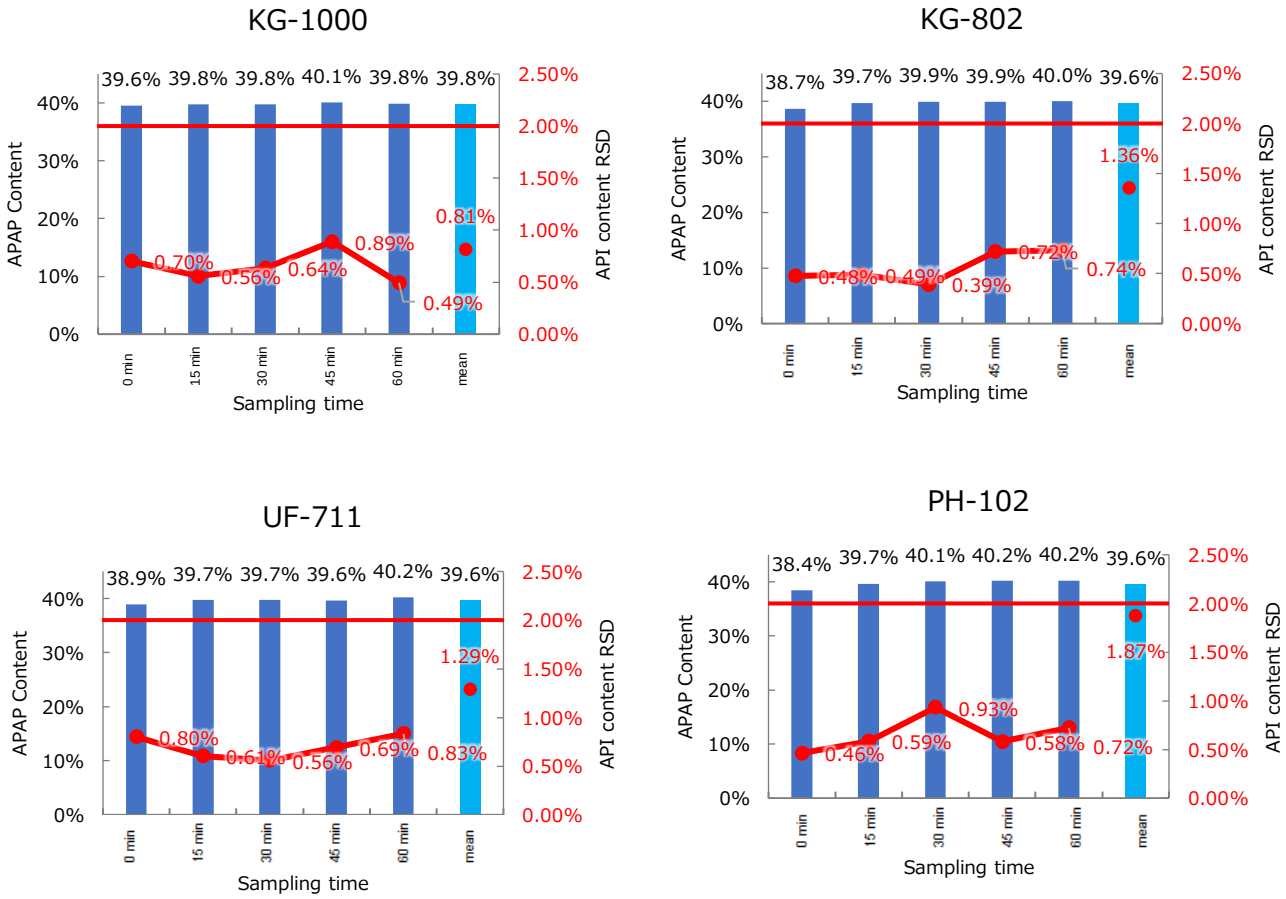



Fig. 7 APAP content and API content RSD for all formulations at each sampling time

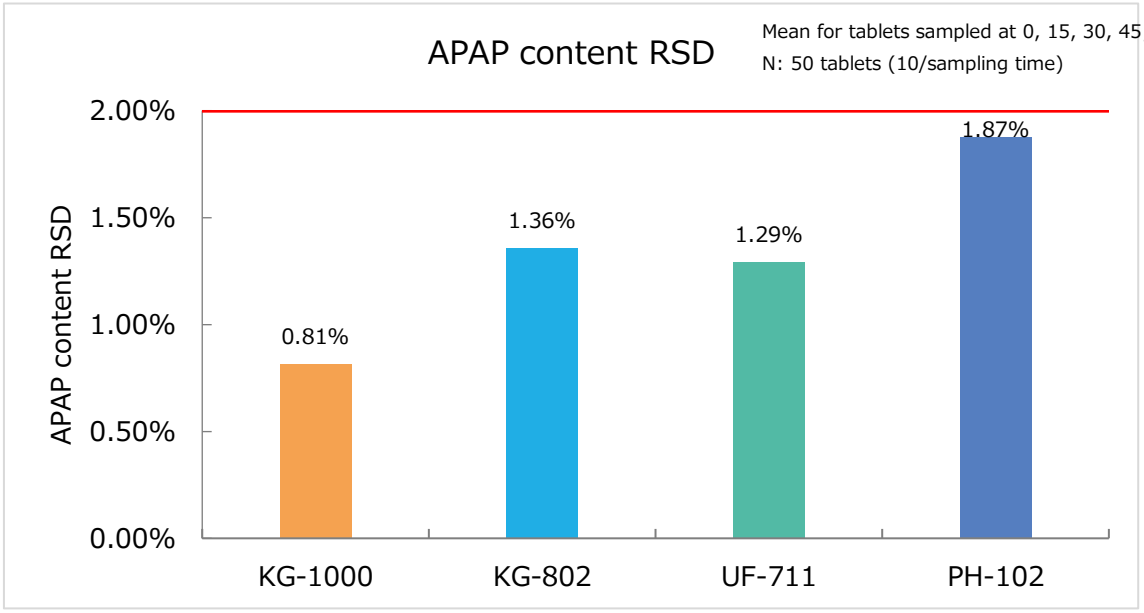



Fig. 8 Mean API content RSD of each formulation

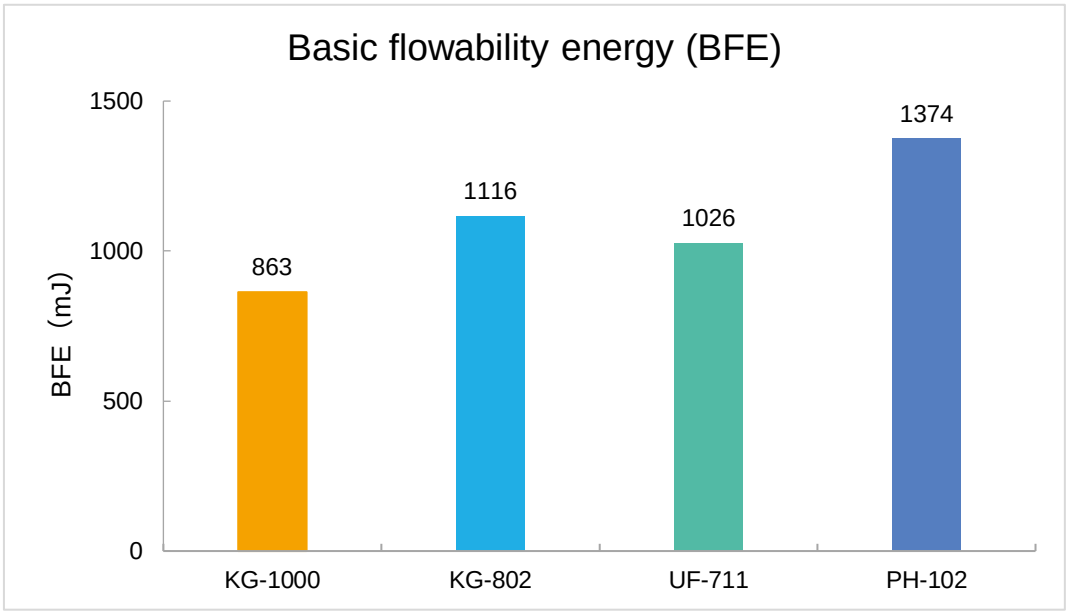



Photo of FT-4 powder rheometer

Source: Spectris's website

Fig. 9 BFE of each Ceolus™ grade

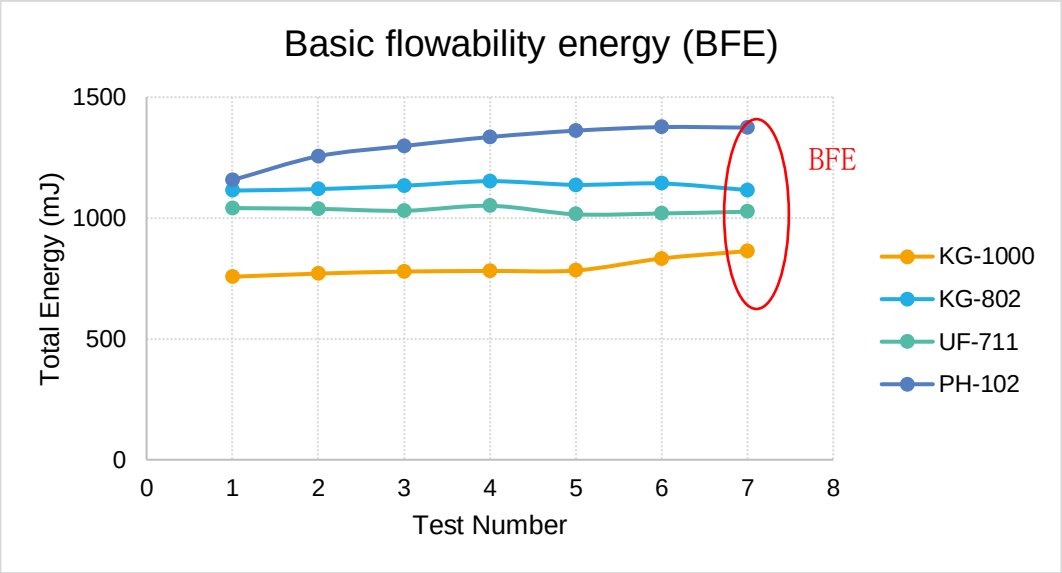



Fig. 10 BFE of each Ceolus™ grade

Fig. 11 shows tablet hardness at each sampling time, and Fig. 12 shows the mean hardness at each sampling time. KG-1000 had the lowest additive volume and the highest hardness. This high hardness is thought to be due to the superior dynamic flowability mentioned above, which contributes to the orientation of fibers within the tablet, thus giving a larger contact area. The changes seen over 60 minutes showed that the hardness of KG-1000, KG-802, and UF-711 remained high, whereas PH-102 tended to decrease in hardness over time, and its hardness RSD also worsened. Being heavy and spherical, PH-102 also showed poor results for dynamic flowability in the BFE measurements, which suggests that its state of mixing worsened over time.

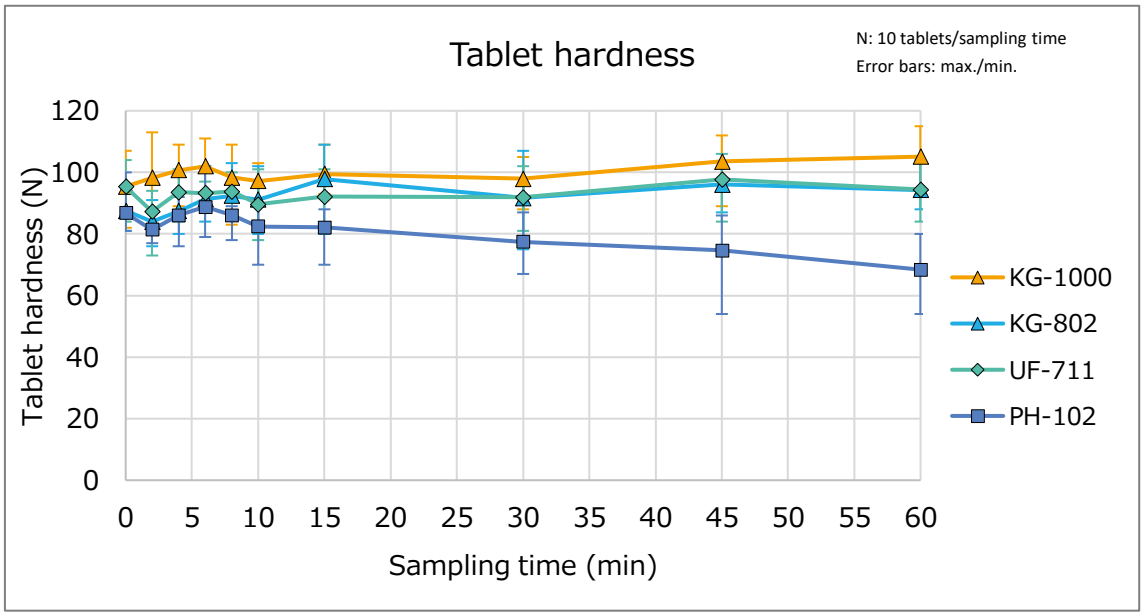



Fig. 11 Mean tablet hardness at each sampling time

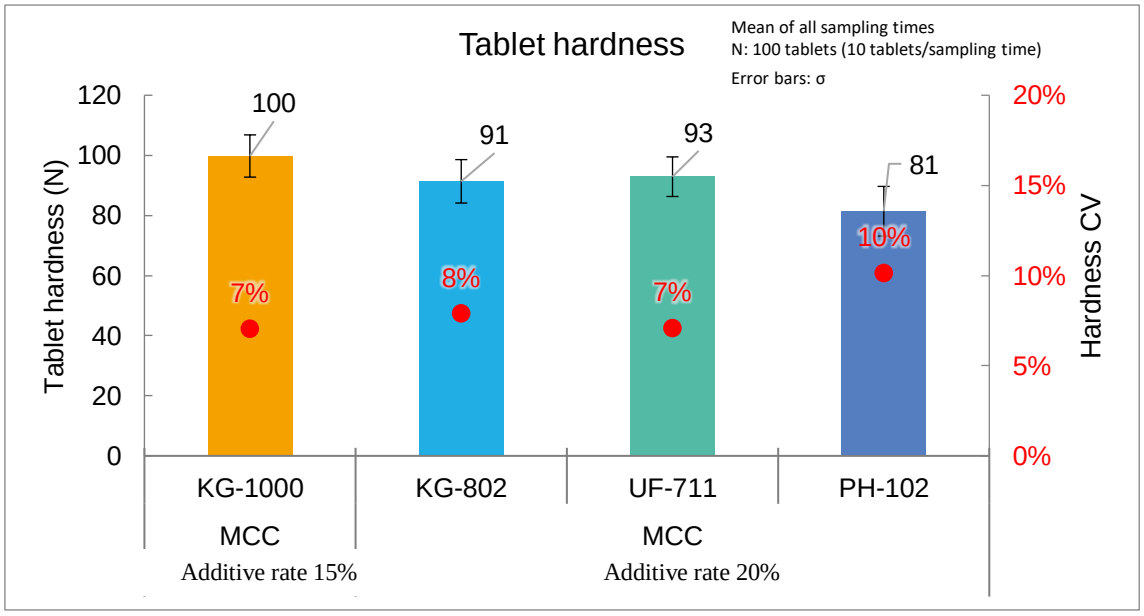



Fig. 12 Mean tablet hardness in each formulation

Fig. 13 shows tablet friability at each sampling time, and Fig. 14 shows the mean friability for all sampling times.

KG-1000, KG-802, and UF-711 met the target of ≤0.20%, but PH-102 did not.

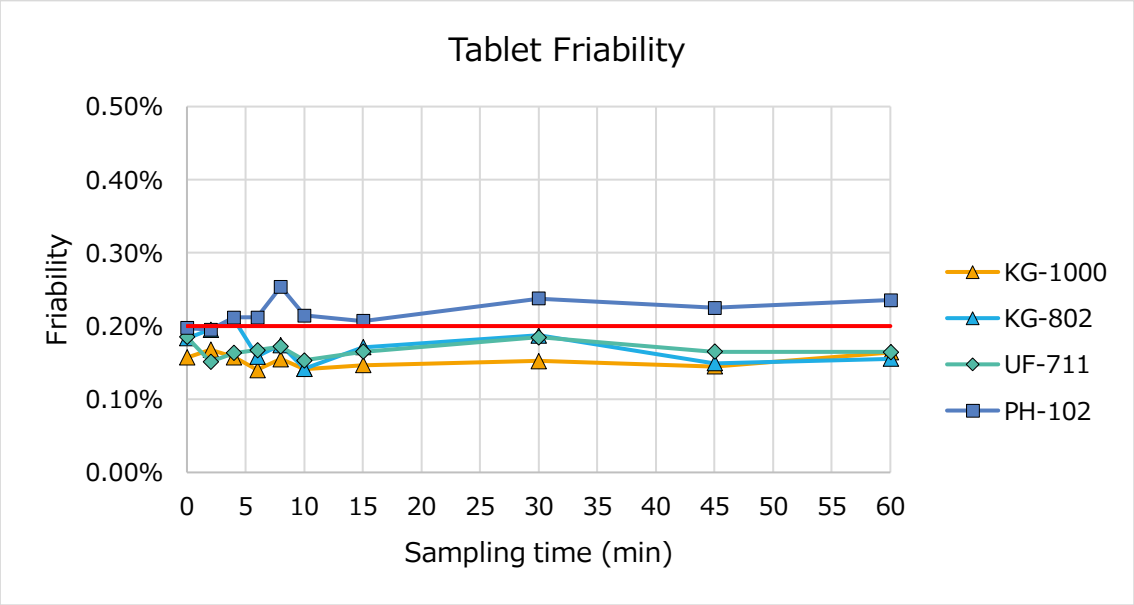



Fig. 13 Tablet friability at each sampling time

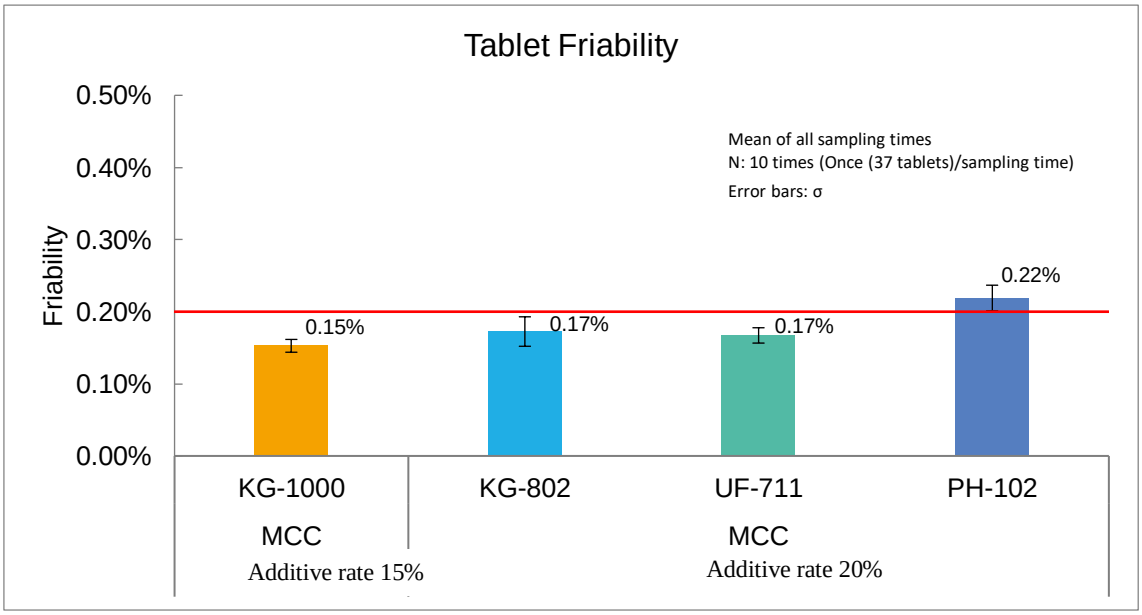



Fig. 14 Mean tablet friability of each formulation

Fig. 15 shows tablet disintegration times at each sampling time, and Fig. 16 shows the mean disintegration time for all sampling times. The results were good in all formulations, with

disintegration in less than 3 minutes, meeting the target of ≤30 minutes.

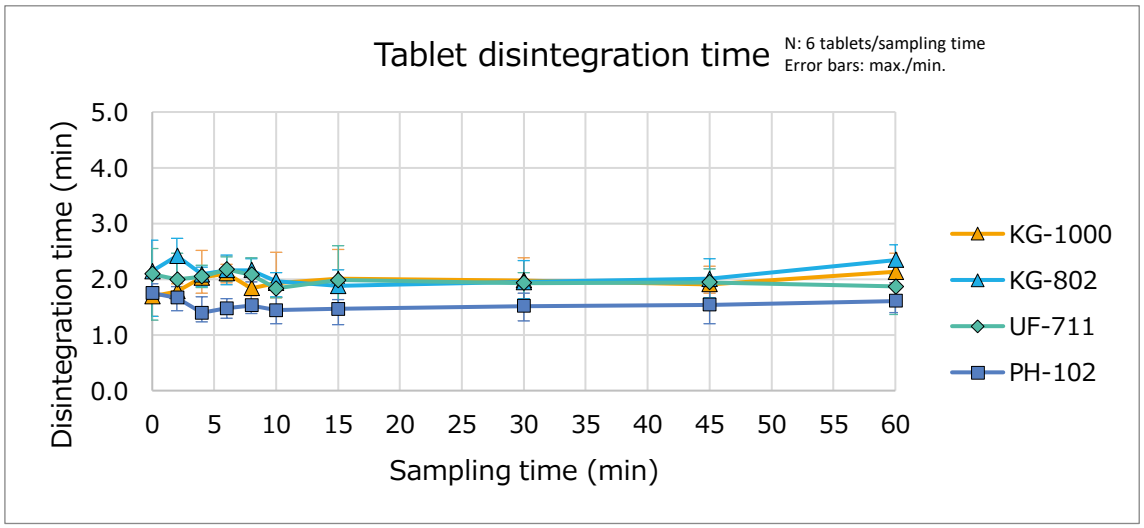



Fig. 15 Tablet disintegration time at each sampling time

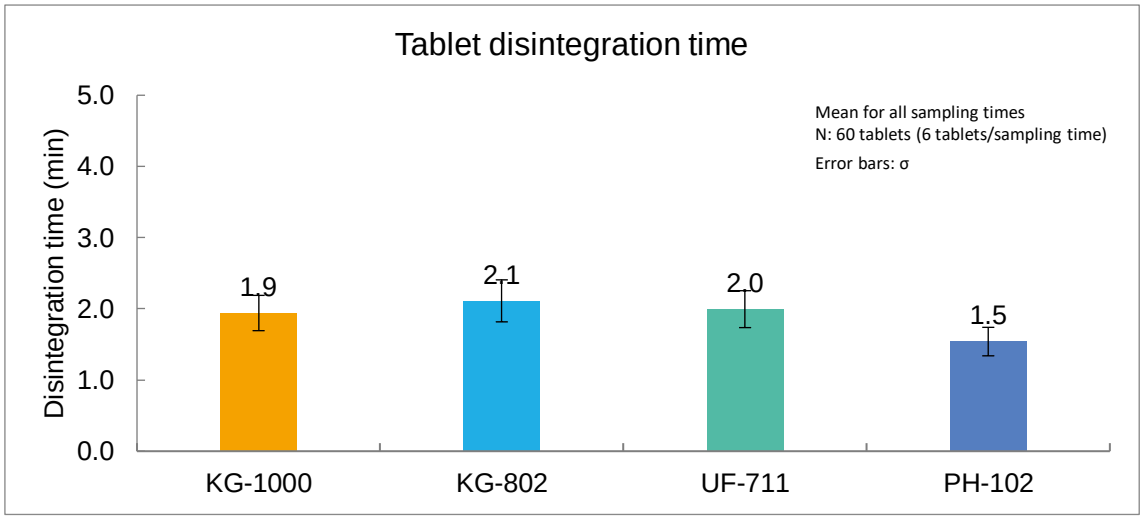



Fig. 16 Tablet disintegration time for each formulation

Fig. 17 shows the results of dissolution testing. The results were good in all formulations, meeting the target of dissolution rate ≥85% after 15 minutes.

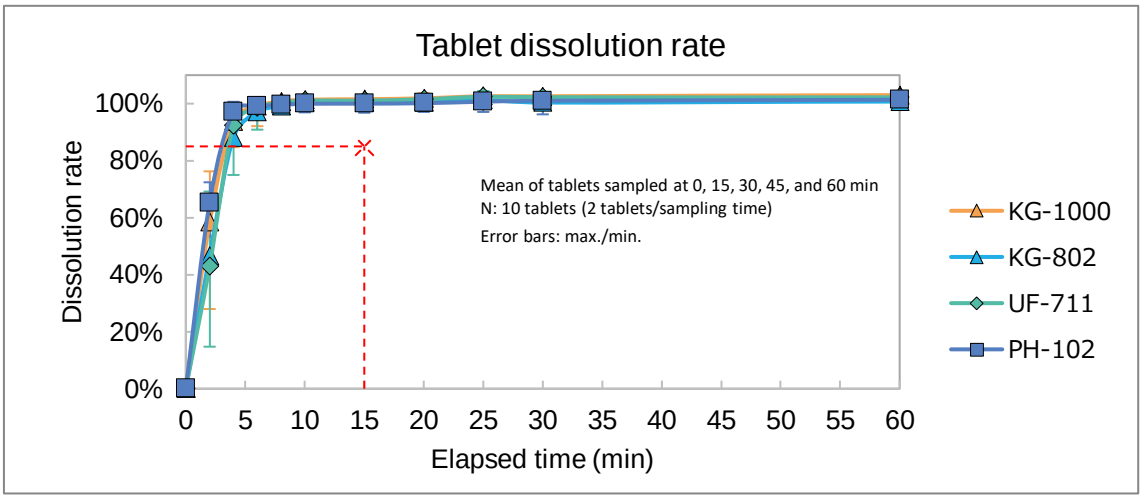



Fig. 17 Tablet dissolution time for each formulation

Table 4 lists the results of the evaluations in this study. All grades met the target values. KG-1000 notably showed the highest compactability and the lowest friability, weight RSD, and API content RSD at lower additive volumes than the other grades.

Table 4. List of evaluation results

| **No.** | | **1** | **2** | **3** | **4** |
|---|---|---|---|---|---|
| Evaluation item | **Target value** | **KG-1000** | **KG-802** | **UF-711** | **PH-102** |
| Tablet weight RSD | <2% | 1.0% | 1.0% | 1.3% | 1.0% |
| API content RSD | <2% | 0.81% | 1.36% | 1.29% | 1.87% |
| Tablet hardness | >50 N | 100 N | 91 N | 93 N | 81 N |
| Tablet hardness RSD | - | 7% | 8% | 7% | 10% |
| Tablet friability | <0.20% | 0.15% | 0.17% | 0.17% | 0.22% |
| Tablet disintegration time | <30 min | 1.9 min | 2.1 min | 2.0 min | 1.5 min |
| Dissolution test Dissolution rate after 15 min | >85% | 100% | 100% | 100% | 99.7% |

## 3. Summary

In this study, the CRA-RIS SYSTEM manufactured by Kikusui Seisakusho Ltd. was used to compare Ceolus™ grades using a formulation containing 40% fine powder-type APAP in a direct compression, continuous manufacturing system, with the goal of determining whether stable continuous manufacturing is feasible and which grade could produce tablets with the best physical properties.

All of the Ceolus™ grades satisfied the target values for physical properties. In particular, the high-performance grades KG-1000, KG-802, and UF-711 had better results for tablet hardness and API content RSD than the PH-102, which is the direct compression standard grade.

Of all these grades, KG-1000 showed higher hardness and superior abrasion resistance, weight RSD, and API content RSD at lower additive volumes, indicating that it is useful for obtaining tablets with good physical properties in direct compression, continuous manufacturing systems using a force feeder.

## 4. Conclusion

It is hoped that this study will contribute to formulation development in continuous manufacturing of tablet using direct compression.


## 5. Acknowledgements

The authors are grateful to Kikusui Seisakusho Ltd. for allowing us to use their continuous manufacturing system equipment for this study.