Comparison of Ceolus™ Grades in Continuous Manufacturing (Wet Granulation)

− Continuous Manufacturing System “Granuformer® Gf-2050”

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1. Introduction

Until now, batch manufacturing has been the main mode of pharmaceutical manufacture: raw materials are input and processed in a stage of the process then removed for input and process in the next stage of the sequence. However, in recent years, manufacturers have explored introducing continuous manufacturing in which the processes from raw material input to removal of the final product are carried out continuously, from the perspective of cutting the space needed for processes and omitting scale-up studies with the aim of reducing the drug development period. The environment for the practical application of continuous manufacturing continues to develop: for example, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has discussed draft guidelines for continuous manufacturing, and equipment manufacturers are also developing continuous manufacturing systems. However, there is still a lack of knowledge on suitable excipients for continuous manufacturing systems.

The aims of this study were to confirm the applicability of Ceolus™ in a continuous manufacturing system and to determine the optimum grade. A comparative study was conducted using the Granuformer® Gf-2050 continuous manufacturing system developed by the Freund Corporation.

2. Experiment

2-1. Raw materials

API: Acetaminophen (APAP)

Excipients: Microcrystalline cellulose (MCC), Ceolus™ PH-101, KG-802, KG-1000, UF-711, UF-702 (Asahi Kasei Corporation)

Excipients: 200 mesh lactose

Disintegrant: Corn starch

Binding agent: Hydroxypropyl cellulose (HPC-L)

Lubricant: Magnesium stearate (Mg-St)

2-2. Experiment Methods

1) APAP micronization

APAP is crushed so that the mean particle size (D50) is 1 μm to 20 μm.

2) Granulation formulation

[Granule] Crushed APAP/lactose (200M)/corn starch/Ceolus™

= 1/62/27/10/3.5 (outer percentage) [wt.%]

Table 1 Granulation formulation

		Test formulations (5)				
Formulation		①	②	③	④	⑤
Drug	Crushed acetaminophen	1%				
Excipient	200 mesh lactose	62%				
	Corn starch	27%				
	Ceolus™ PH-101	10%				
	Ceolus™ UF-702		10%			
	Ceolus™ UF-711			10%		
	Ceolus™ KG-802				10%	
	Ceolus™ KG-1000					10%
	Binding agent/HPC-L (outer percentage)	3.5%				

3) Granulation conditions

Equipment: Continuous manufacturing system Granuformer® Gf-2050 (Freund Corporation)

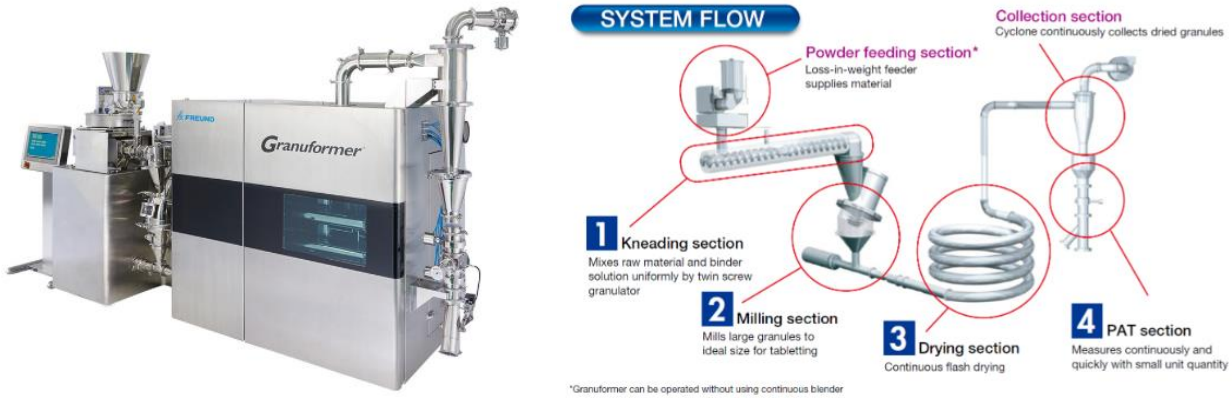

Fig. 1 Continuous Manufacturing System Granuformer® appearance and system flow chart

Source: “Freund Corporation Granuformer® Catalog”

Granulation conditions: Processing rate 15 kg/h

40 kneading paddles, displacement angle 45°, speed 100 rpm

Water addition ratio 30, 35, 37, 40 wt.%

Granulator 1,000 rpm, screen φ3 mm

Drying conditions: Supplied air temperature 120 °C, air flow 8.5 m^3/min

4) Tableting conditions

[Tableting formulation] Granule/Mg-St = 99.5/0.5 [wt.%]

Tablet press: LIBRA2 (Kikusui Seisakusho Ltd.)

Tableting conditions: Open feeder, 12 punches, 30 rpm, 200 mg tablets, φ8 mm–12R

5) Experiment flow

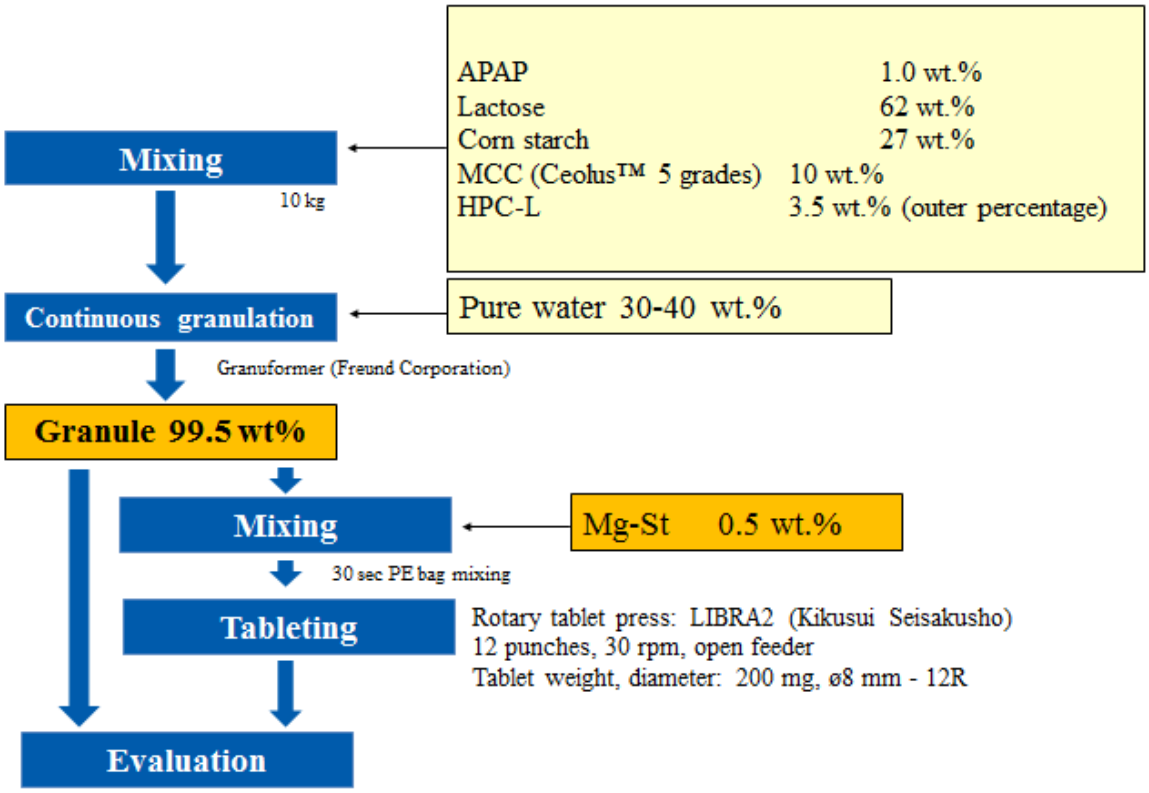

Fig. 2 Experiment flow

(Set points)

• Granule size: 150±30 μm

• Tablet hardness: 60 N, 80 N, 100 N (max. tableting pressure 25 kN)

6) Evaluation method

(Powder properties)

• Water absorption rate: The weight of MCC powder was determined. Next, the MCC powder was put into pure water so that it absorbed the water, and the MCC was then separated by centrifugation and collected.

The amount of water absorbed was calculated from the difference between the MCC weight after water absorption and the MCC powder weight before water absorption, using the formula shown below.

Water absorption rate [%] = (amount of pure water absorbed / initial weight of MCC powder) ×100

(Granule properties)

• Granulability: The degree of blockage in the granulator at completion of granulation was checked visually.

• Granule size: Particle size was measured using sieves with openings of 500, 300, 250, 212, 150, 106, 75, and 45 μm, with reference to the measurement method described in the Japanese Pharmacopoeia (18th Edition), and the particle size with a measured cumulative weight ratio of 50% was taken as the mean particle size.

• Bulk density: This was measured using a Scott Volumeter, with reference to the Japanese Pharmacopoeia (18th Edition).

- Repose angle: This was measured using a Sugihara-style repose angle measuring instrument, with reference to the Japanese Pharmacopoeia (18th Edition).
- Moisture: This was measured using an infrared moisture meter FD-240 (Kett Electric Laboratory Co. Ltd.) with powder weight 10 g, drying temperature 80 °C, and heating time 15 min.

(Tablet properties)

All of the following were evaluated with reference to the measurement methods described in the Japanese Pharmacopoeia (18th Edition).

- Tablet hardness (compactability): The mean value was taken from 10 tablets measured using Tablet Tester 8M (Dr. Schleuniger Pharmatron).
- Friability test: This was measured using PT F30ERA (Pharma Test) with 33 tablets, drum rotation speed 25 rpm, and rotation time 4 min.
- Disintegration time: The mean value was taken from 6 tablets measured using the TN-40HS disintegration tester (Toyama Sangyo Co., Ltd.) with pure water (37 °C) and no disc.
- API content RSD: The tablets were dissolved in pure water, insoluble material was filtered (pore size 0.45 μm, Membrane solutions), and the tablet APAP content was then determined by the absorbance method (λ = 244 nm).
  The coefficient of variation was defined as standard deviation/mean value of absorbance of 10 tablets × 100.
- Dissolution time: The mean value was taken from two tablets measured with JP liquid I (liquid volume 900 mL) using a DT-610 dissolution tester (JASCO Corporation).

2-3. Test results

2-3-1. Granulability

As shown in Table 2, by regulating the amount of water added during granulation, it was possible to achieve granulation to the target granule size (150 ± 30 μm) without the granulator becoming blocked. During granulation, when the water absorption rate of the excipients was higher, granulator blockages were less likely to occur, and granulation could be achieved without granulator blockages over a wider range of water addition. Of the five Ceolus™ grades tested, KG-1000, which had the highest water absorption, tended to have a wider water addition range of 30-40%.

Table 2 Granulability

MCC	Added water volume [%]				Absorption rate of MCC [%]
	30	35	37	40	
PH-101	○	○	–	×	200
KG-802	○	○	×	–	230
UF-702	○	○	▲	–	240
UF-711	○	○	–	▲	240
KG-1000	○	○	–	△	**290**

(Evaluation criteria)
×: Early granulation stage (0-6 min), ▲: Clogging in early granulation stage (6-11 min), △: Clogging in late granulation stage (11-16 min), ○: No clogging (Granulation time 16 min), —: Not tested

*When three grades with different water absorption rates (PH-101, UF-711, and KG-1000) were tested at 40% water addition, clogging was seen with KG-1000, which has the highest water absorption. KG-802 and UF-702, which have lower water absorption than KG-1000, were therefore tested with the water addition reduced to 37%.

2-3-2. Granule properties

1) Granule size (D50)

In all cases, the granule size was generally within the target value at 35-40% water addition relative to the powder raw material (Fig. 3).

Compared to the other grades, KG-1000, with its high water absorption rate, had a wider water addition range and tended to have relatively small variation in granule size relative to the amount of water added.

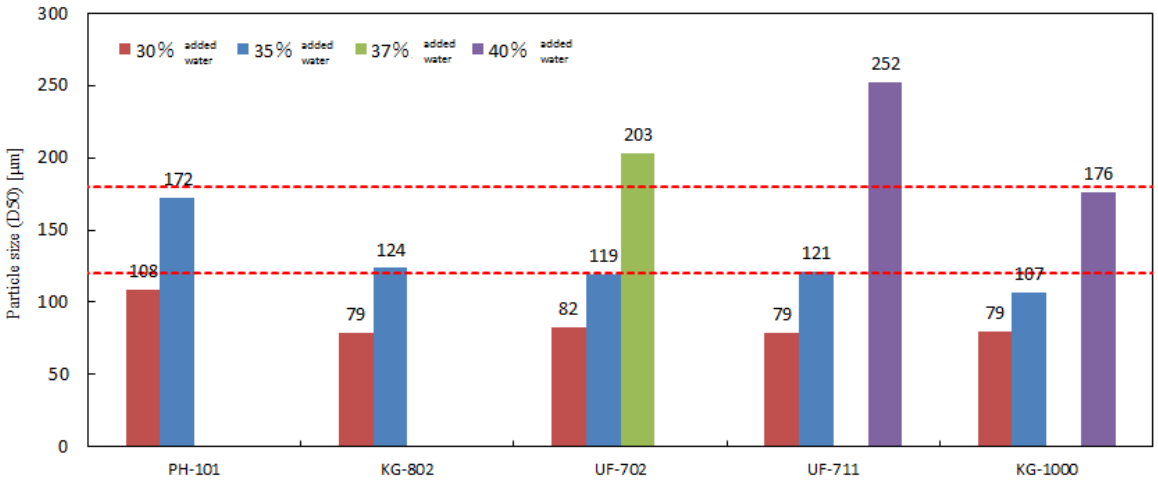

Fig. 3 Granule size (D50)

2) Bulk density and repose angle

Granule bulk density was within the range of 0.4-0.5 g/cm^3 in all cases. Comparison when the same volume of water was added showed that KG-1000 was slightly lighter of the five Ceolus™ grades (Fig. 4). In addition, the repose angle was below 45° in all grades, and granules with good flowability were obtained (Fig. 5). Granule moisture was within the range of 2-4% in all grades (Fig. 6).

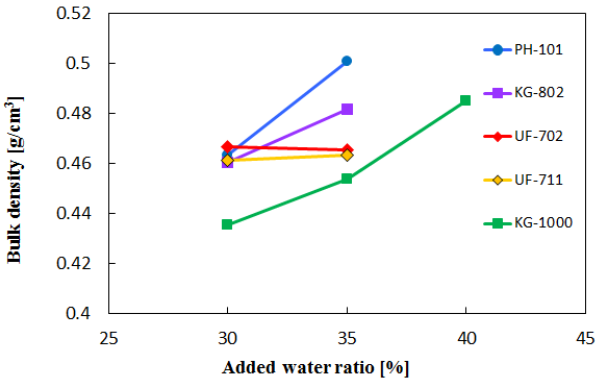

Fig. 4 Bulk density

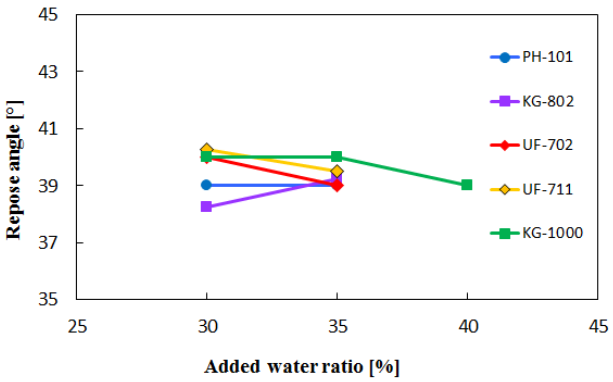

Fig. 5 Repose angle

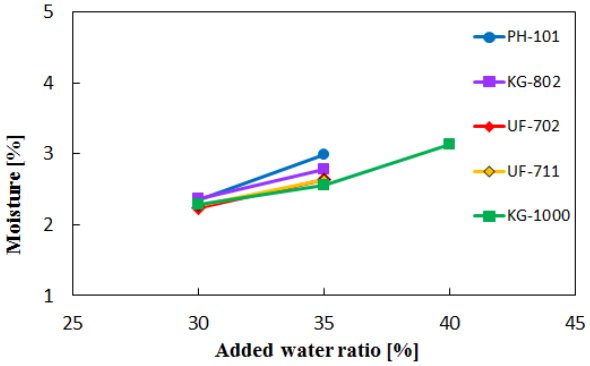

Fig. 6 Moisture

2-3-3. Tablet properties

1) Results for tablet hardness

When the granule diameters were matched (150 ± 30 μm), the high compactability grade KG-1000 showed the highest compactability (Fig. 7).

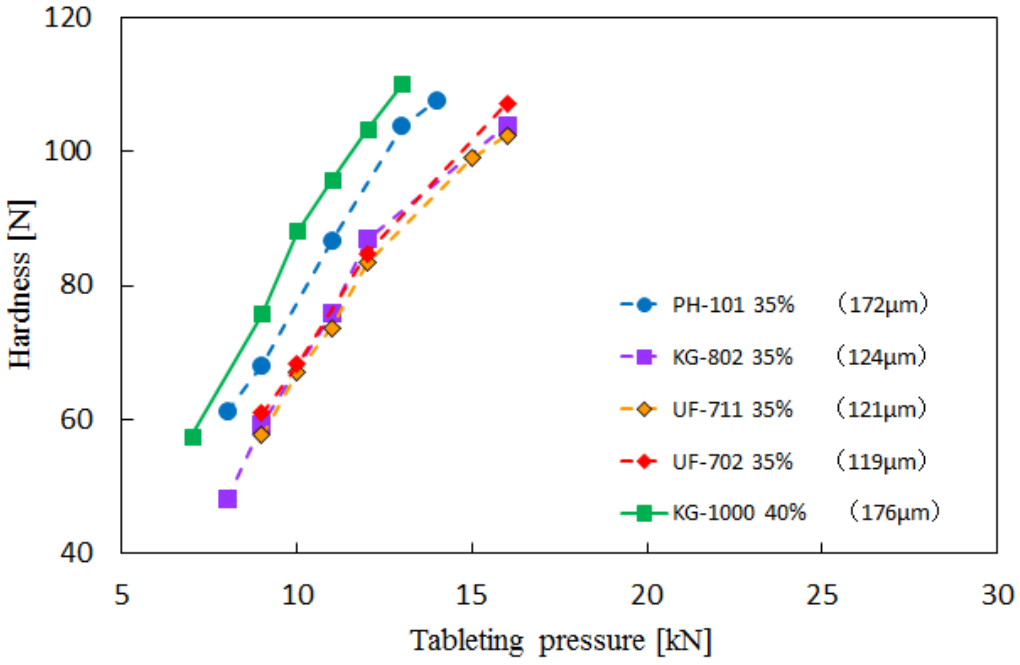

Fig. 7 Tablet hardness

2) API content RSD

API content RSD was compared using tablets with a hardness of around 80-90 N. The results were good, with API content RSD below 2% for all additives (Fig. 8).

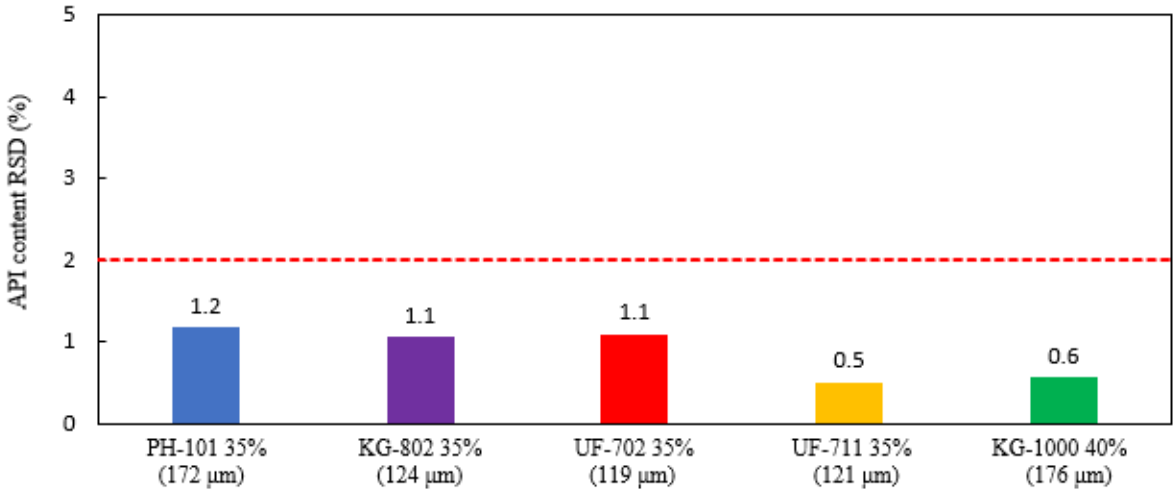

Fig. 8 API content RSD

3) Friability

The results were good, with tablet friability ≤0.5% for all additives at all test pressures (Fig. 9).

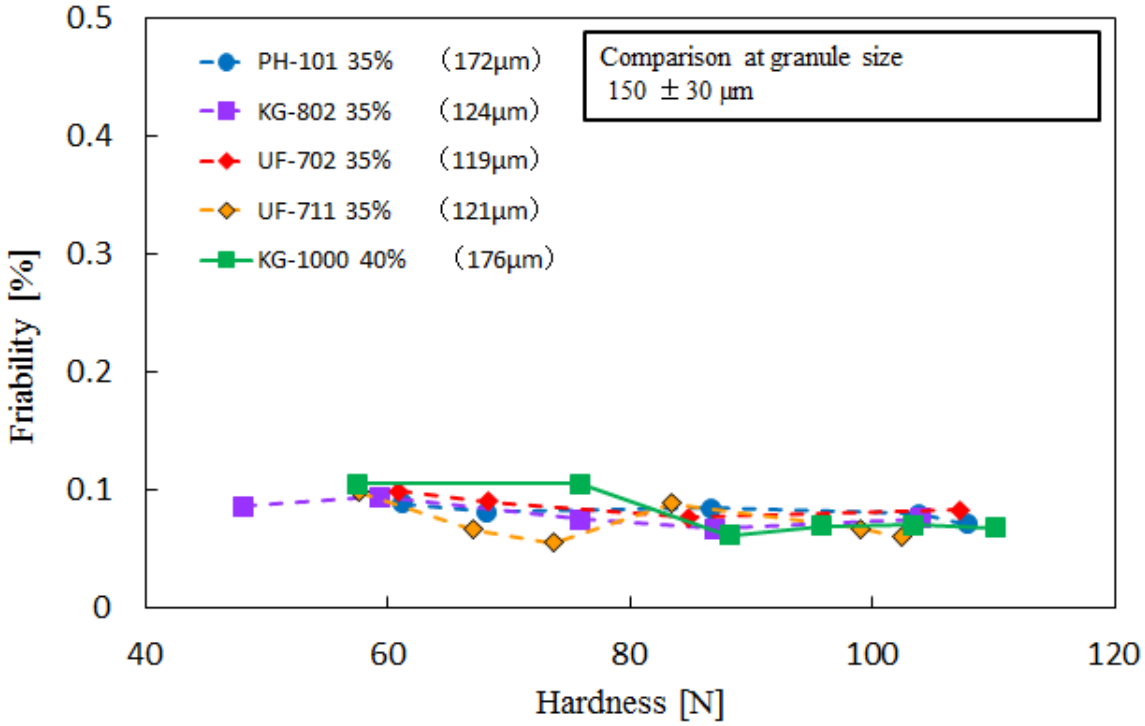

Fig. 9 Friability

4) Disintegration

The results were good, with a disintegration time ≤5 min in all tests, for all additives at all test pressures (Fig. 10).

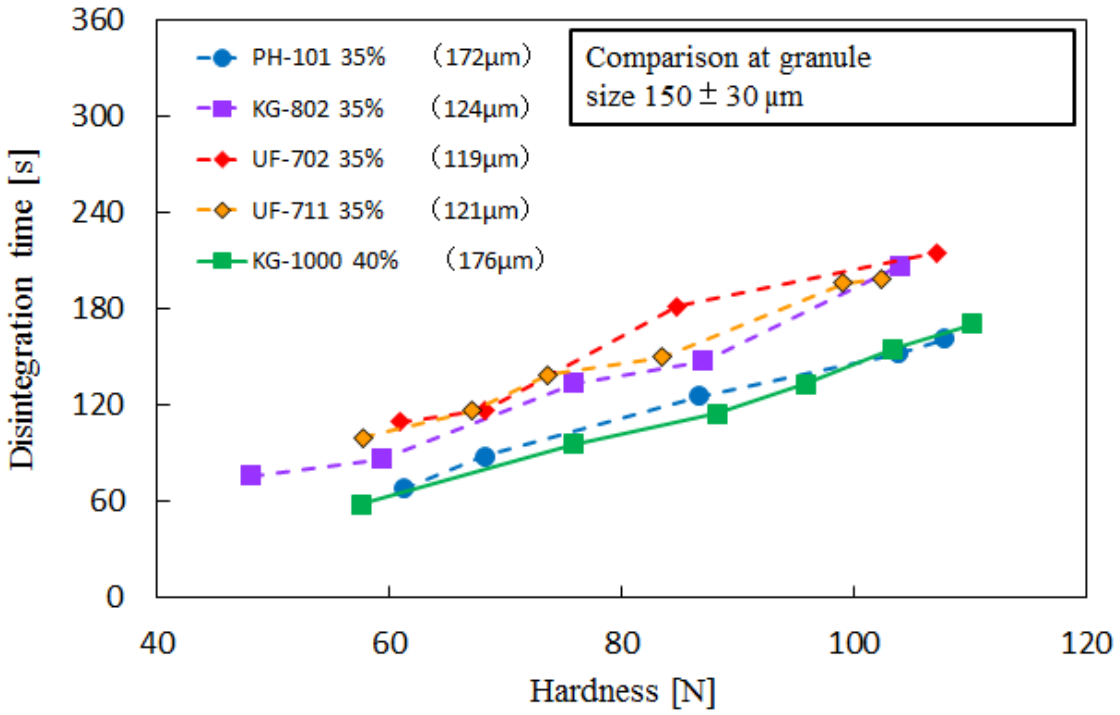

Fig. 10 Disintegration

5) Dissolution

Dissolution was compared using tablets with a hardness of around 80-90 N. Results were good, with dissolution meeting the targets (15 min, ≥85%) in all cases (Fig. 11).

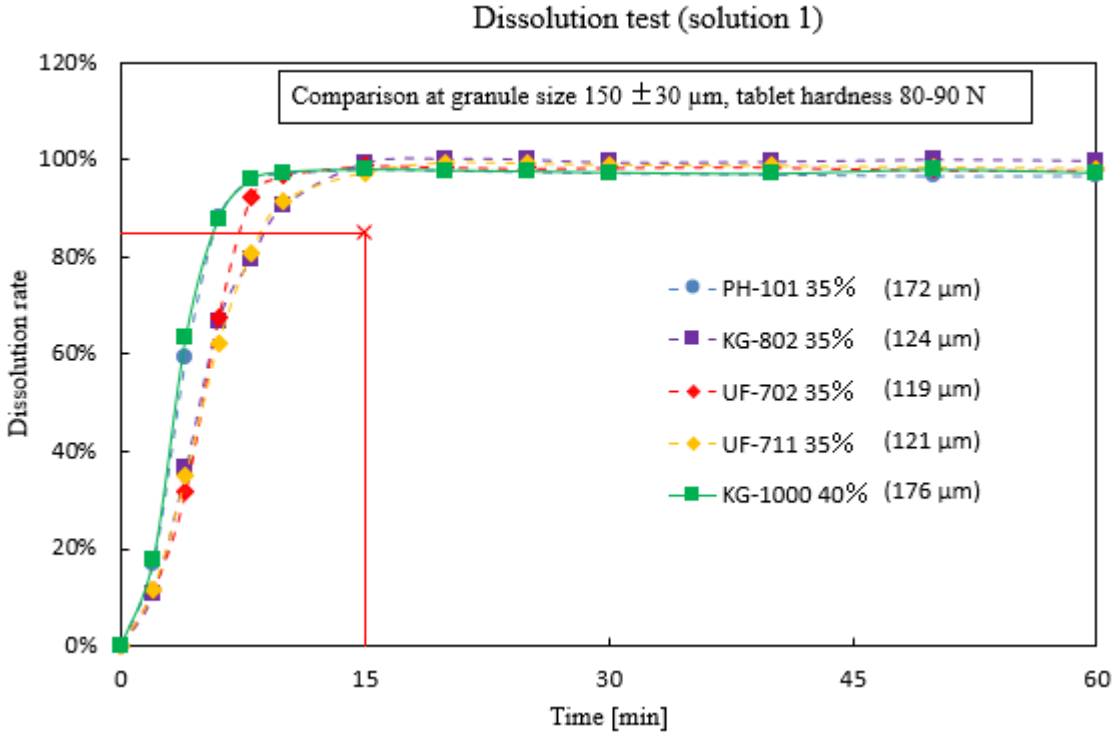

Fig. 11 Dissolution

3. Summary

In this study, five Ceolus™ grades were compared and evaluated in continuous manufacturing using the Granuformer® Gf-2050 continuous manufacturing system made by the Freund Corporation. All five Ceolus™ grades tested in this study could be granulated to the target granule size by adjusting the added volume of water, and the tablet properties also met the practical target values. Of these grades, KG-1000, which has a high water absorption rate, had the widest water addition range, suggesting that granule size could be easily controlled during granulation. In addition, KG-1000 showed superior balance of compactability, disintegration, and dissolution in tests at the same pressure. These results demonstrated that KG-1000 was the optimum Ceolus™ grade in this study.

4. Conclusion

The applicability of Ceolus™ grades to continuous manufacturing was demonstrated using the Granuformer® Gf-2050 continuous manufacturing system. It is hoped that this study will aid in pharmaceutical development using the Granuformer® Gf-2050 and other continuous manufacturing systems. A patent application (application no: 2021-040567) has been submitted for the technology described in this study.

5. Acknowledgements

The authors are grateful to the Freund Corporation for their cooperation in the use of the continuous manufacturing system equipment and in data acquisition during this study.