Comparative Study of Microcrystalline Cellulose Grades on Process Robustness in High Shear Granulation

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INTRODUCTION

Within the Quality by Design (QbD) framework, understanding how critical process parameters (CPPs) affect critical quality attributes (CQAs) is essential for establishing a robust design space (DS). High-shear granulation (HSG) involves multiple CPPs that significantly influence granule size and tablet dissolution behavior, making excipient selection a key factor in improving process robustness. Microcrystalline cellulose (MCC), widely used in HSG for its high water absorption capacity, contributes to the control of granule growth and tablet performance. Therefore, this study investigated the effect of MCC powder property differences on CPP sensitivity by evaluating two representative CQAs — granule size (D50) and 15-min dissolution (Q15) — using a Box–Behnken design as a QbD-based experimental approach to assess process robustness in HSG.

EXPERIMENTS

Table 1. Powder properties and morphology of MCC grades.
SEM images were taken at ×200 magnification with a 100 µm scale bar.
FIB-SEM images show particle cross-sections.

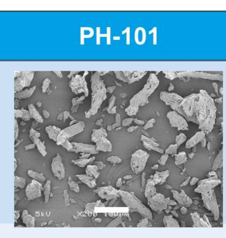
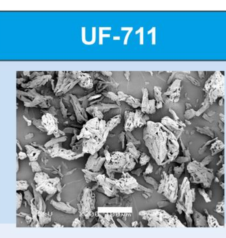
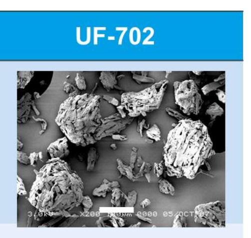
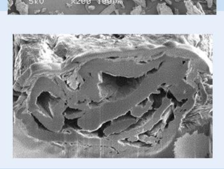
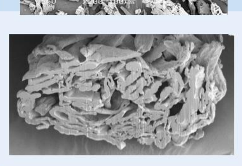
Ceolus™ grades	PH-101	UF-711	UF-702
Morphology of particles			
Cross-sectional morphology			
Particle size (µm)	50	50	90
Loose bulk density (g/mL)	0.29	0.22	0.29
Water absorption (%)	200	240	240

Table 2. Composition per tablet.

Ingredients	wt%
Ethenzamide	29.3
MCC (Ceolus™ PH-101, UF-711, UF-702)	9.8-19.6
Lactose	48.9-58.7
Hydroxypropyl cellulose (HPC)	1.2
Magnesium Stearate (MgSt)	1.0

Formulation : Ethenzamide / MCC / Lactose / HPC = 30/ 10-20 / q.s./ 1.2 (wt%)

Granulation
High-shear granulator : VG-10 (Powrex, Japan)
Impeller speed: 280 rpm / Chopper speed : 3000 rpm
Premixing time : 5 min / Granulation time : 3-7 min
Binder : HPC solution
Binder addition : Hopper feed / Added water content : 18.5-22.5%
Batch size : 1 kg

Drying
Fluid-bed dryer : MP-01 (Powrex, Japan)
Inlet air temperature (set) : 75℃
Outlet air temperature (endpoint) :40 ℃
Airflow : 70-80 m^3/h

Milling
Centrifugal mill : ZM-200 (Retsch GmbH, Germany)
Rotor speed : 6000 rpm
Screen size : 1 mm
+710 µm fraction milled and recombined with −710 µm fraction

Luburication
Blending : Granules / MgSt = 99 / 1(%)
Mixing : 30 s in poly-ethylene bag

Tableting
Single-punch tablet press (Ichihashi Seiki Co., Ltd., Japan)
Tableting speed : 30 tablets / min
Tablet weight / type : 180 mg / Φ8 mm-12R
Compression force : 8.5-11.5 kN
Target tablet hardness : 50 N

Evaluation
Granule size (D50), Dissolution rate at 15 min (Q15)
Dissolution test conditions : purified water (900 mL), paddle rotation speed of 50 rpm.

Figure 1. Experimental procedure.

Table 3. Experimental conditions for the Box–Behnken design.

Run	MCC loading (wt%)	Added water content (wt%)	Granulation time (min)
1	15	18.5	3
2	15	18.5	7
3	15	22.5	3
4	15	22.5	7
5	10	18.5	5
6	20	18.5	5
7	10	22.5	5
8	20	22.5	5
9	10	20.5	3
10	20	20.5	3
11	10	20.5	7
12	20	20.5	7
13	15	20.5	5

RESULTS

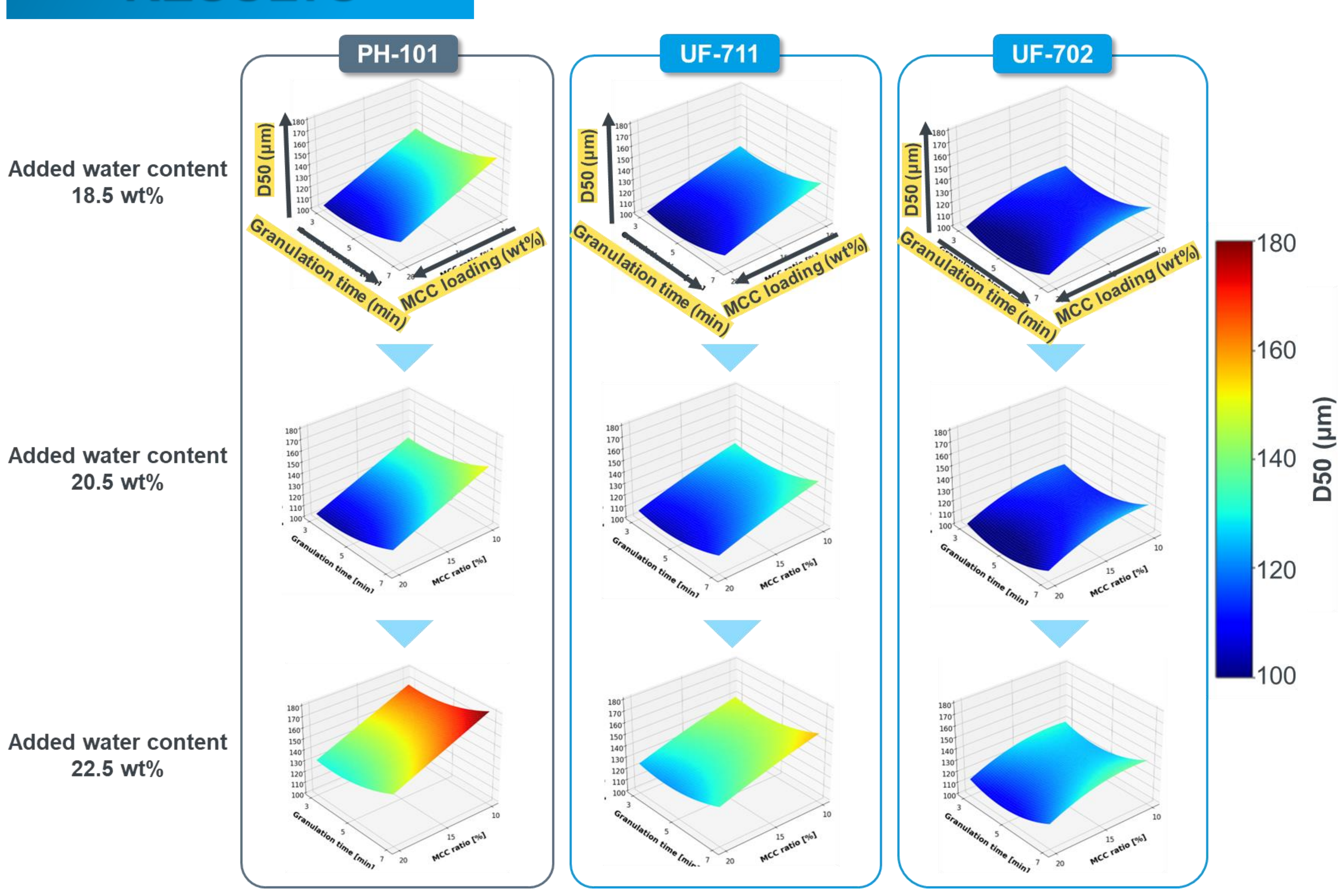


Figure 2. Response surface plots of D50 at different added water contents.

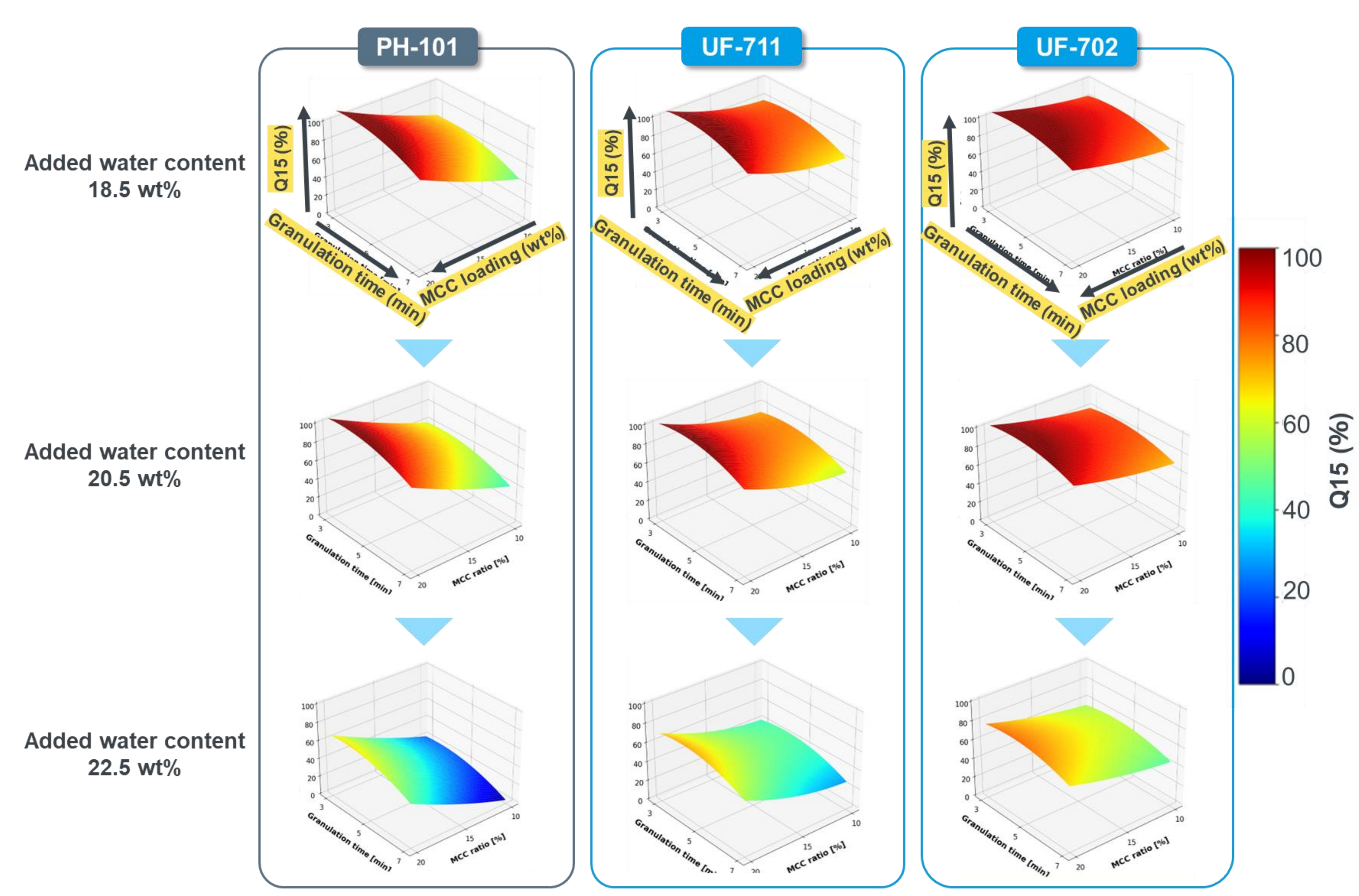


Figure 3. Response surface plots of Q15 at different added water contents.

Across the experimental region, lower MCC loading, higher added water content, and longer granulation time tended to increase D50, while higher MCC content, lower water content, and shorter granulation time improved Q15. Compared with PH-101, the UF grades exhibited smaller CPP-induced variation in both D50 and Q15. Among all grades, UF-702, characterized by its larger particle size and higher porosity, showed the most stable performance across formulation and process changes.

CONCLUSION

The impact of MCC grade on the HSG process was evaluated by comparing Ceolus™ PH-101, UF-711, and UF-702 using a QbD approach.UF grades, characterized by their porous structure and water absorption capacity, showed smaller CPP-induced variation in both D50 and Q15 compared with PH-101. In particular, UF-702, which has a larger particle size, exhibited the most stable granule growth and dissolution profile. These results indicate that employing UF-702 can improve process robustness and may contribute to broadening the DS in HSG processes.

CONTACT INFO

Product Information

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