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Comparative Study of Suitability for Wet Continuous Manufacturing Process Using MCC with Different Characteristics - Part 2

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PURPOSE

Continuous manufacturing systems are increasingly favored for their ability to eliminate the process scale-up and reduce production costs. The continuous wet granulation method integrates raw material supply, hydration, granulation, drying, and tableting within a single system. It is essential to prevent process stagnation due to material clogging during continuous granulation. Moreover, achieving desired physical properties of the granules, especially particle size and distribution, are critical as they influence tablet characteristics such as drug release and weight variation. Effective formulation design is crucial to meet these requirements.

Previously, we presented a comparison of Microcrystalline Cellulose (MCC) grades using the Granuformer® GF-2050 system (Freund Corp., Japan). This study extends our investigation to the CTS-MiGRA SYSTEM (Powrex Corp., Japan), exploring its efficacy in continuous wet granulation.

METHODS

Table 1. MCC & Corn Starch grades and powder properties

General Name	MCC (Ceolus™)				Corn Starch
Grade	PH-101	UF-702	UF-711	KG-802	-
Particle Size (D_{50}, μm)	50	90	50	50	14
Bulk Density (g/mL)	0.29	0.29	0.22	0.21	0.52
Angle of Repose (°)	45	34	42	49	55
Water Absorption (%)	200	240	240	230	60
SEM Image (×500)					

Table 2. Formulations (Percentages are wt%)

Sample	Grade	A	B	C	D	E
Ethenzamide (ETZ)	-	30	30	30	30	30
Mannitol	-	50	50	50	50	50
Ceolus™	PH-101	20	-	-	-	-
	UF-702	-	20	-	-	-
	UF-711	-	-	20	-	-
	KG-802	-	-	-	20	-
Corn Starch (CS)	-	-	-	-	-	20
Total	-	100	100	100	100	100
HPC	L	1.5	1.5	1.5	1.5	1.5

Figure 1. CTS-MiGRA SYSTEM

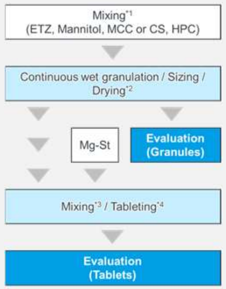

Figure 2. Procedure of continuous manufacturing process

*1 High shear granulator VG-100 (Powrex Corp., Japan) Blade: 190 rpm, Cross screw: 3000 rpm, Time: 3 min
*2 CTS-MiGRA SYSTEM (Powrex Corp., Japan)
Granulation conditions; Granulation rate: 250 g/min, Tilt angle: 0°, Water content: 10-30 wt%
Drying conditions; Input temperature: 85 ºC, Airflow: 1.0 m^3/min, Product temperature: 43 ºC
*3 99.5 parts of granules and 0.5 parts of Mg-St were mixed for 30 s in a PE bag.
*4 Rotary tablet press 102i (Fette Compacting GmBH)
Force feeder: 10 rpm, Tablet size/ type: 180 mg/ φ8 mm-12R, Tableting speed: 30 rpm (30 punches)

RESULTS

Table 3. Granulation results and water addition rate

Water Addition Rate (wt%)	Formulations A PH-101	B UF-702	C UF-711	D KG-802	E CS
15.0	Accept	ND	Accept	Accept	Accept
17.5	ND	ND	ND	ND	Accept (MWA)
20.0	Accept	Accept	Accept	Accept	Marginal
25.0	Accept (MWA)	Accept	Accept (MWA)	Accept (MWA)	ND
30.0	Marginal	Accept (MWA)	Marginal	Marginal	ND

Ceolus™ UF-702 formulation (Formulation B) allowed maximum water addition up to 30 wt%, while formulation E containing corn starch only allowed 17.5% of water addition. Porous particle morphology of UF-702 contributed to significantly higher absorption of water than corn starch (60%).

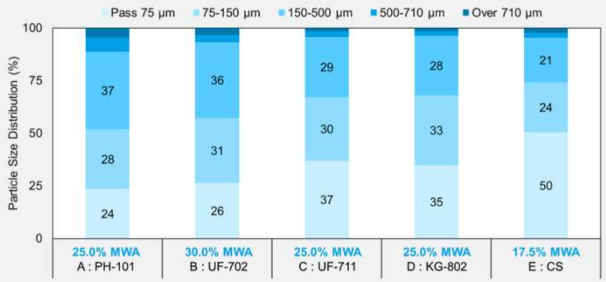

Figure 3. Particle size distribution of all granules

Overall, formulations with MCC resulted in significantly lower amounts of fines compared to the corn starch formulation. The UF-702 formulation (Formulation B), in particular, demonstrated a low level of fines at higher water addition of 30 wt%, indicating a wider wet granulation processing window.

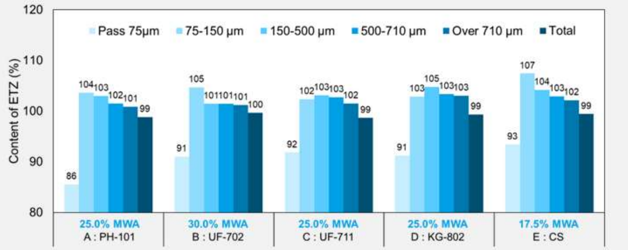

Figure 4. ETZ content in size-sieved granules

It was found that the ETZ content in the small particles was the lowest across all formulations. Based on the results so far, the maximum permissible water addition is highest for formulation B, indicating its excellent robustness in the granulation process. Additionally, formulation B also showed a reduced generation of small particles. Considering these results, the UF-702 formulation (Formulation B) is recommended for use in this system.

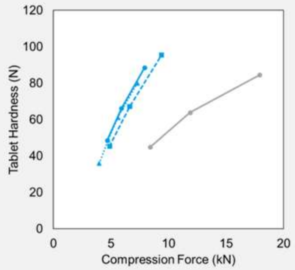

Figure 5. Tablet hardness vs Compression force

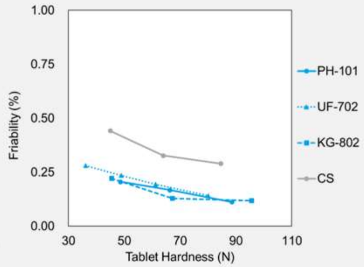

Figure 6. Friability vs Tablet hardness

Upon examination of the tablet manufacturing process, formulations containing MCC required lower compression pressures (5-7 kN) compared to the CS formulation (>10 kN) to achieve a tablet hardness of 60 N. Additionally, formulations containing MCC demonstrated superior tablet friability compared to the CS formulation, although no significant differences were observed between the MCC grades.

CONCLUSION

This investigation clearly shows the impact of MCC particle morphology on continuous wet granulation. Overall, MCC formulations resulted in lower levels of fines, a more uniform particle size distribution, and better tablet properties compared to the corn starch formulation. The current study highlights the impact of the porous particle morphology of UF-702, which contributed to greater water absorption and a wider processing window for continuous wet granulation. Our evaluations suggest that the unique particle morphology of MCC helps to enhance the continuous wet granulation process.

REFERENCE

M. Higuchi, K. Tsuru, Comparative Study of Suitability for Wet Continuous Production Process Using MCC with Different Characteristics, Poster M1130-08-51, AAPS PharmSci 360, Orlando, October 2023.

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