Changing MCC type (without composition change) to alter the mechanical properties of tablets obtained

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Introduction

- Excipients are an essential part of tablet composition, especially in high-drug-loaded formulations.
- High-drug-loaded formulations of poorly flowable and poorly compactible substances are manufactured using granulation methods, including roll compaction (**RC**).
- Microcrystalline cellulose (**MCC**) is one of the most common excipients for tablets and for the RC granulation method.
- Nevertheless, the viscoelastic properties of MCC differ from grade to grade.
- Consequently, changing the grade of MCC in the formulation can drastically influence the resulting properties of granules and tablets.
- Thus, **the aim of this study** was to compare Ceolus™ PH-101 (an MCC grade that is close to its properties to other PH-101 grades) with the functional MCC grades (Ceolus™ KG-1000, KG-802, and UF-711).
- For this purpose, the effect of MCC level (20, 30, and 40 wt.%) and roll compaction pressures (3, 4, and 5 kN/cm) on the granule size distribution, tablets' tensile strength, friability, and disintegration time were investigated.

Materials

- Poorly compactible substance – **Metformin HCl** (Auro Laboratories, Tarapur, India);
- **Ceolus™ KG-1000, KG-802, UF-711,** and **PH-101** (Asahi-Kasei, Tokyo, Japan) were used as to different MCC grades;
- glidant – **silica dioxide** (Syloid® 244FP; Grace GmbH, Worms, Germany);
- lubricant – **sodium stearyl fumarate** (SSF; Nippon Soda Co. Ltd., Tokyo, Japan).

Conditions	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9
Composition for RC-granulation *(variable)*									
MCC (wt.%)	20			30			40		
Metformin HCl (wt.%)	80			70			60		
Additional extra-granular excipients *(constant)*									
Silica dioxide (wt.%)	0.5			0.5			0.5		
SSF (wt.%)	2.0			2.0			2.0		
RC Conditions *(variable)*									
RC Force, kN/cm	3	4	5	3	4	5	3	4	5

Results

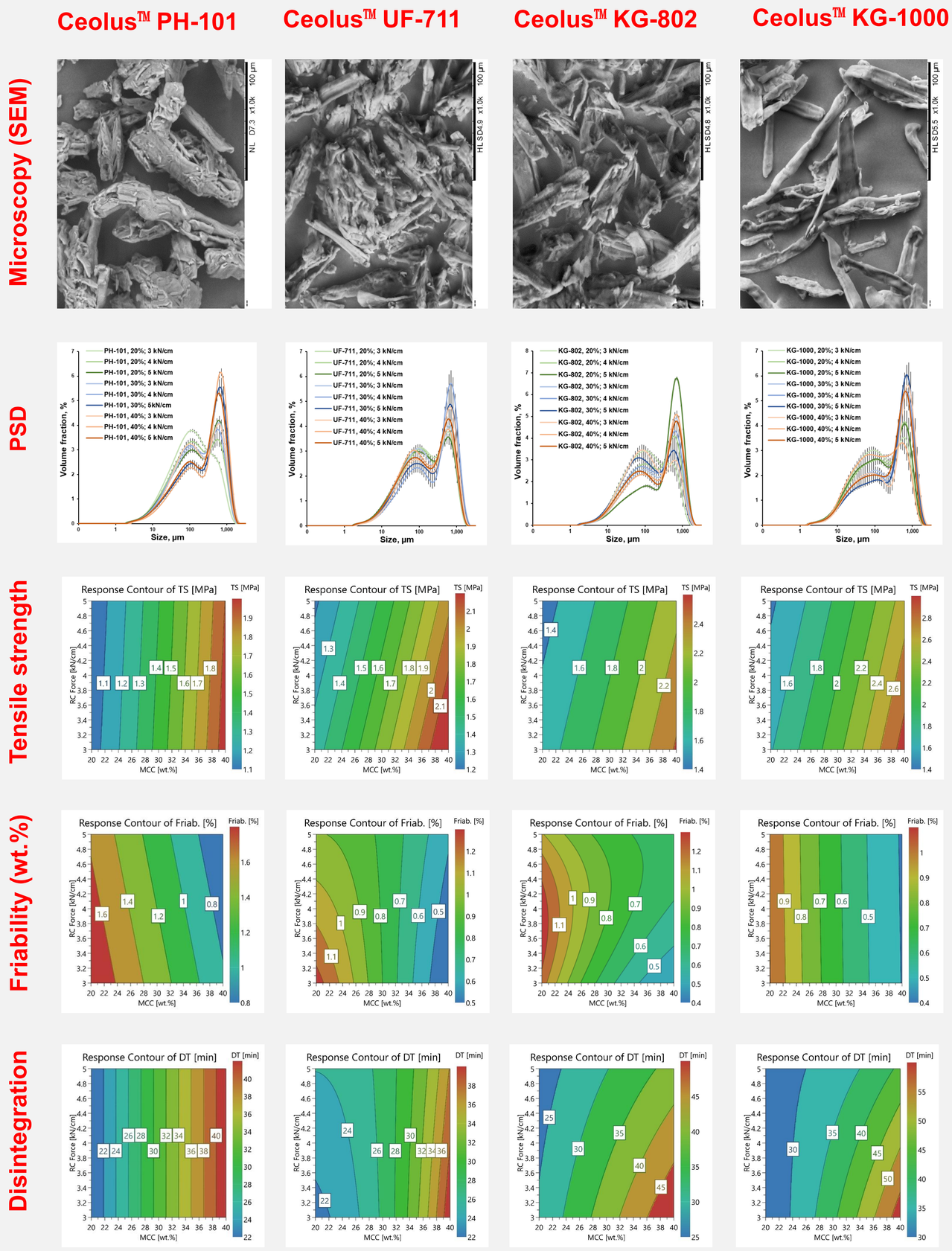
- Different types of Ceolus™ have different morphologies and microstructures (**SEM**).
- Powder mixtures with different MCC concentrations and different MCC types resulted in bimodal but different particle size distributions as a function of roll compaction pressure.
- In general, the increase in Ceolus™ portion and RC-force increases granule size.
- In our experiment, the tensile strength of 2 MPa can be achieved starting from 39 wt.% of Ceolus™ PH-101, 36 wt.% of UF-711, 32 wt.% of KG-802, and 28 wt.% of KG-1000.
- While formulations with Ceolus™ PH-101 and KG-1000 didn't show the interaction of factors (variables), the interaction of these factors for Ceolus™ UF-711 and KG-802 was obvious and reflected a complex dependence. In our experiment, the mass loss below 1 wt.% can be achieved starting from 32 wt.% of Ceolus™ PH-101, 21 wt.% of KG-802, 20 wt.% of UF-711, and below 20 wt.% of KG-1000, respectively.
- To show how the properties of different MCC types themselves influence the disintegration time, tablets were prepared without any disintegrating agent. The addition of a disintegrant in concentrations up to 5 wt.% can drastically decrease the disintegration time.
- The increase of MCC content in tablets resulted in the increase of the disintegration time for all Ceolus™ types used.

Conclusion

- Changing the MCC grade, along with the concentration and RC-force, significantly influenced the RC-granules particle size distribution, tablet mechanical properties (incl. tensile strength and friability) and disintegration time.
- The obtained results demonstrated that Ceolus™ KG 1000 clearly outperformed other Ceolus™ grade in terms of the mechanical properties of metformin HCl tablets prepared using the roll compaction granulation method.
- The biggest difference was observed between Ceolus™ KG 1000 and PH-101, while Ceolus™ UF-711 and KG-802 set the intermediate position.

Methods

- **Preparation of mixtures for granulation.** The formulations were prepared according to **Table.** Materials were mixed for 10 minutes, sieved through the screen with a mesh size of 1.0 mm, and mixed for 10 minutes again (DVC Developer; Comasa, Barcelona, Spain).
- **Roll Compaction.** The powder mixture was processed with a roll compactor (WP 120; Alexanderwerk GmbH, Remsheid, Germany). The batches of 1`500 g were prepared with crosshatched surface rolls at different roll compaction forces of 3, 4, and 5 kN/cm (**Table**) and throughput of 140-150 g/min. The ribbons (at 3 mm rolls' gap) were calibrated by hammer mills via mesh sizes of 1.6 mm and 0.8 mm for the first and second stages of the calibration, respectively.
- **Particle Size Distribution** (PSD). The PSD as well as the D10%, D50%, and D90% were determined by a laser diffraction particle size analyser using an 'Aero S' module for dry dispersions (Mastersizer 3000, Malvern Instruments, Malvern, UK) at the specified settings: feed rate of 60%; hopper gap of 1.5 mm; air pressure of 0.8 bar. Approximately 15-20 g of the sample was used for each repetition (n = 3).
- **Tableting Mixture Preparation.** Materials (silica dioxide and sodium stearyl fumarate) were separately sieved through the screen with a mesh size of 0.5 mm. Granules were mixed with silica and SSF for 5 min (**Table 1**).
- **Tableting.** Powder mixtures were tableted with 11.28 mm flat punches to obtain a target mass of 500 mg. Tableting was performed with a compaction simulator with automatically the feeding shoe (STYL'One Nano; Medelpharm, Beynost, France). Compression cycles simulated a small rotary press at 70 rpm.
- **Tablet Hardness Measurement and Tensile Strength Calculation.** The tablet thickness (h) and diameter (d), as well as tablet hardness (breaking force, F) were measured (n=10) by a tablet tester (ST50 WTDH; Sotax AG, Aesch, Switzerland) immediately after the compaction. The tensile strength (τ, MPa) was calculated by employing the following equation: $\tau = (2F)/(\pi d h)$
- **Tablet friability** test was conducted using 20 tablets and an automatic drum (FRV 100i; Copley, Nottingham, UK) at a fixed rotation speed and test duration (25 rpm for 4 min).
- **Disintegration time** of tablets was determined with a disintegration tester (ZT 732; Erweka GmbH, Langen, Germany) in 900 mL of water at 37±0.5℃. Six tablets (n=6) were tested for each formulation.
- **Statistically based design of experiments (DoE).** A three-level full factorial design with one additional center-point was applied (Table 1) using DoE software MODDE® Pro (ver. 13.1.0.687; Sartorius AG, Umeå, Sweden).



Funding: This study was funded by Asahi-Kasei (Tokyo, Japan) and conducted by the Leading Research Group (Faculty of Pharmacy, Rīga Stradiņš University, Riga, Latvia); Research Agreement Contract No. 3-L-9/56/2025 (signed on 2025.10.22).

Mohylyuk V, Kukuls K, Frolova AJ, Buczkowska EM, Shmyrova J. Changing microcrystalline cellulose type (without composition change) to alter the mechanical properties of tablets obtained. Compaction Simulation Forum; Lisbon, Portugal; 2026.06.01-03.