Effect of microcrystalline cellulose (MCC) type and roll compaction force on the mechanical properties of tablets containing a high dose of poorly compactible substance

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Introduction

- Tablets are the most popular dosage form, while roll compaction is a continuous process that allows for the organization of the manufacturing of solid dosage forms in a continuous manner with a small footprint and flexible batch size. There is a list of commercially available MCC grades that can be used for the roll compaction granulation of the drug substance with the following tableting. It is expected that upon roll compaction and tableting, different MCC grades will ensure different granules and tablet properties.
- 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).

Methods

- **Preparation of mixtures for granulation.** The formulations were prepared according to **Table 1.** 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 1**) 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).

Table 1

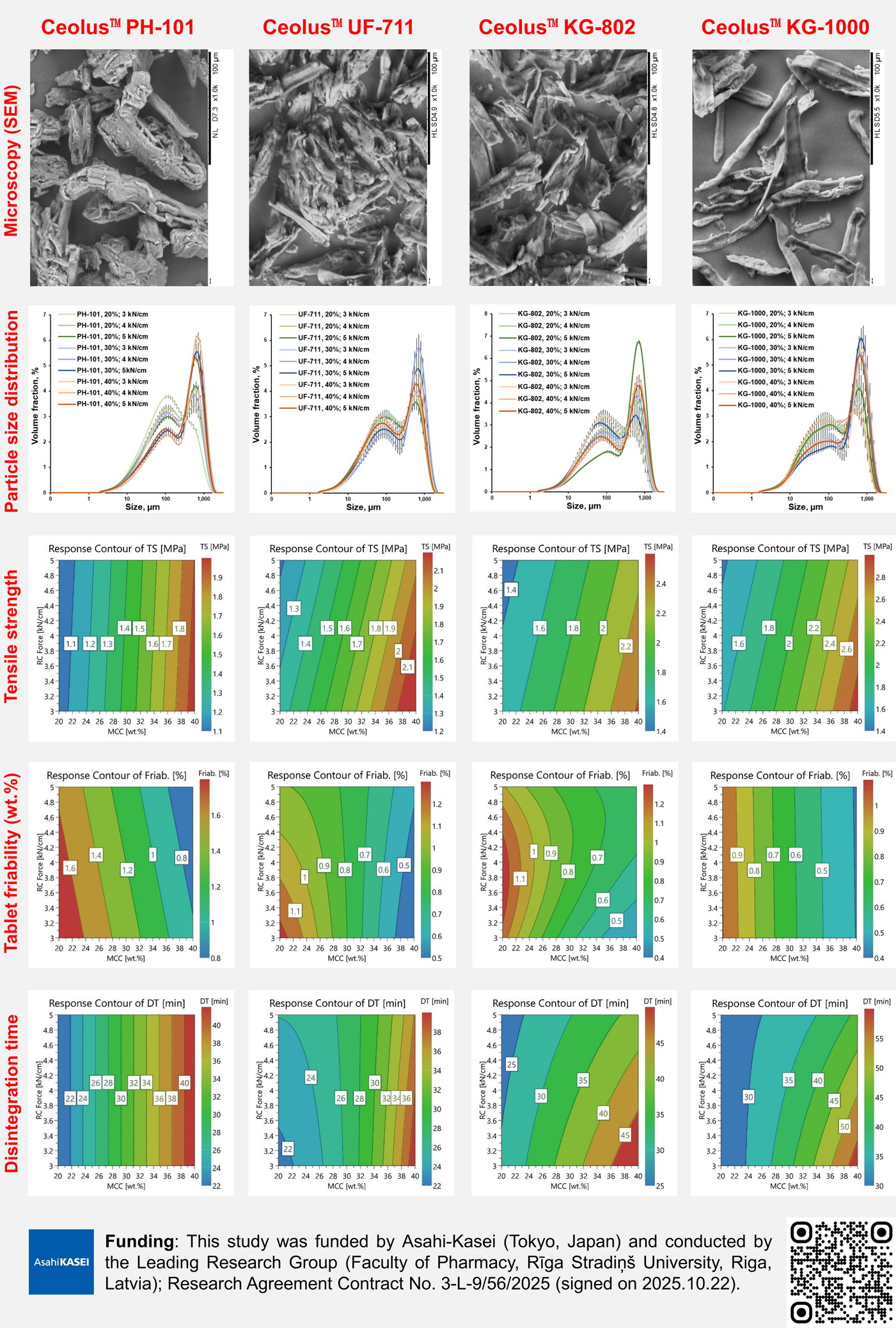
Conditions	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9
Composition for RC-granulation *(variable)*									
MCC (wt.%)		**20**			**30**			**40**	
Metformin HCl (wt.%)		80			70			60	
Additional extra-granular excipients *(constant)*									
Silica dioxide (wt.%)		0.5			0.5			0.5	
SSF (wt.%)		2.0			2.0			2.0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

Results & Discussion

- 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

- In this study were successfully demonstrated the effects of Ceolus™ types, Ceolus™ concentration, and RC-force on 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.



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