Effect of microcrystalline cellulose (MCC) grade on the properties of twin-screw melt granulated formulations of ascorbic acid

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Introduction

- The agglomeration of fine powders during the twin-screw melt granulation (TSMG) occurs due to the softening or melting of thermal binders, consolidation by kneading (applied mechanical forces) and cooling to room temperature along with formation of solid bridges of solidified binder with relatively low temperature melting peak (M_p).
- Continuous melt granulation is gaining popularity because it does not require the solvent removal, shortening the processing time and decreasing the number of critical stages.
- While the effect of binder, binder concentration and granulation conditions on the properties of TSMG processed formulations is presented in the scientific literature, the effect of functional binders as MCC was not well described yet.
- **The aim** of this investigation was to prepare immediate -release tablets of ascorbic acid by continuous TSMG technique and to assess the effect of MCC grade on the properties of granules and tablets.

Materials

- L-ascorbic acid (batch #S03003-041; Sigma-Aldrich, UK) was used as model drug,
- while **Kollisolv® PEG 8000** (BASF SE, Germany) was used as binder.
- "Vitamin C, 500 mg, immediate-release tablets" (**Boots IR**) were used for the comparison and were distributed by Boots Company PLC (UK).
- As a functional filler were used MCC grades (**Fig. 1**) as
  - **Ceolus™ KG-1000**, **Ceolus™ KG-802**, **Ceolus™ UF-711**, and **Ceolus™ UF-702** (Asahi Kasei Corp., Japan),
  - "**MCC A**" (standard grade obtained from another company), and
  - "**MCC B**" (fine particle grade obtained from another company).

Methods

Thermogravimetric analysis (TGA). 5-10 mg samples were heated from room temperature (RT) to 250℃ at a heating rate of 10℃/min in the nitrogen gas flow at 50 mL/min (Q50; TA Instruments, UK).

Differential Scanning Calorimetry (DSC). 5–10 mg sample was heated from RT to 200 or 250℃ at a heating rate of 10℃/min (Q20, TA Instruments, USA) using open aluminum pans in the nitrogen gas flow at 40 mL/min. The data were analyzed using TA instruments universal analysis software (Version 4.5A; TA Instruments, USA).

Powder X-Ray Diffraction (pXRD). Samples were tested with an X-ray diffractometer (Mini-Flex II; Rigaku Corp., Japan) with Cu Kα radiation (30 kV) and 15 mA in the angular range (2 θ; theta degree) from 3 to 60 theta degrees at 2 s/step rate.

Scanning electron microscopy (SEM). Samples were investigated with a scanning electronic microscope (TM3030; Hitachi High-Technologies Corp., Japan) in a vacuumed environment at 15 kV.

Twin-screw melt granulation (TSMG). Ingredients were weighed and mixed using mortar and pestle in accordance with **Table 1**. Formulations were processed with horizontal 10 mm benchtop co-rotating twin-screw extruder (L/D 20:1; Microlab; Rondol Tech. Ltd., France) equipped with conveying elements only at feeding rate of 1.5 g/min, at screw speed of 120 rpm, at 140℃ processing temperatures.

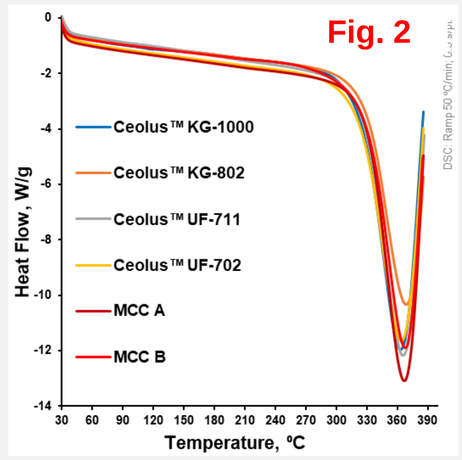
The particle size distribution (PSD) incl. D_{50} was determined by sieving method.

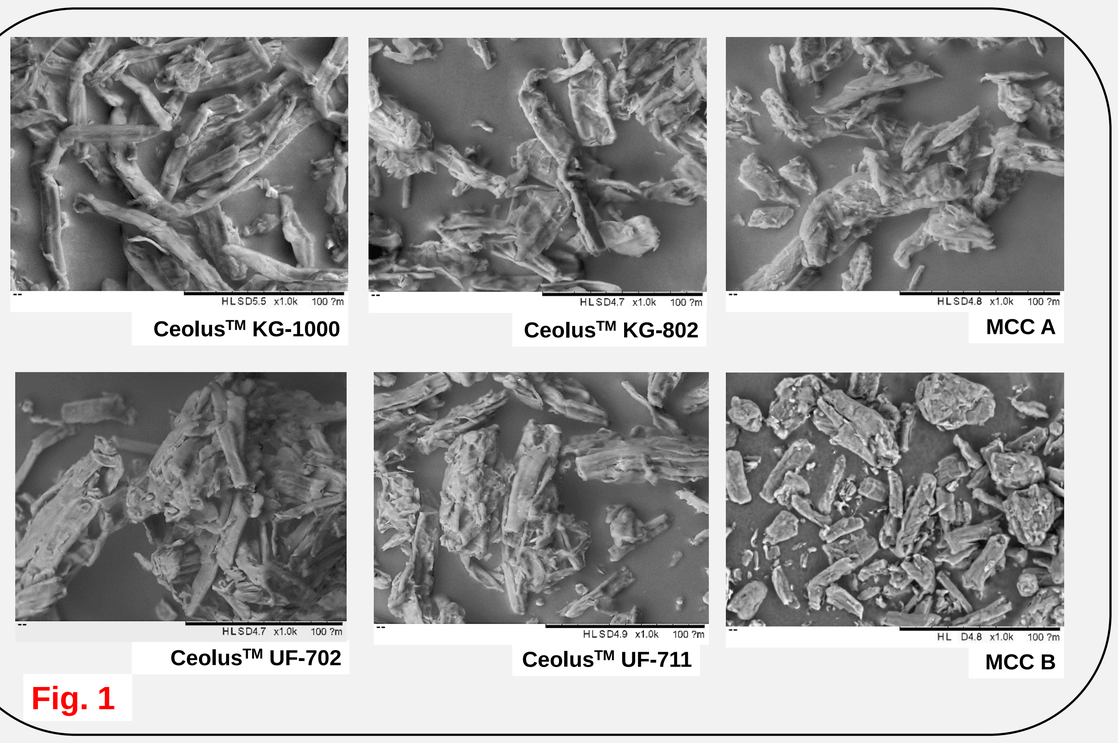
Tablets (Flat-faced; 11mm diameter) were prepared using twin-screw melt granulated formulations with hydraulic press (5 s dwell time) and **tablet hardness** was tested (TBH 125; ERWEKA GmbH., Germany).

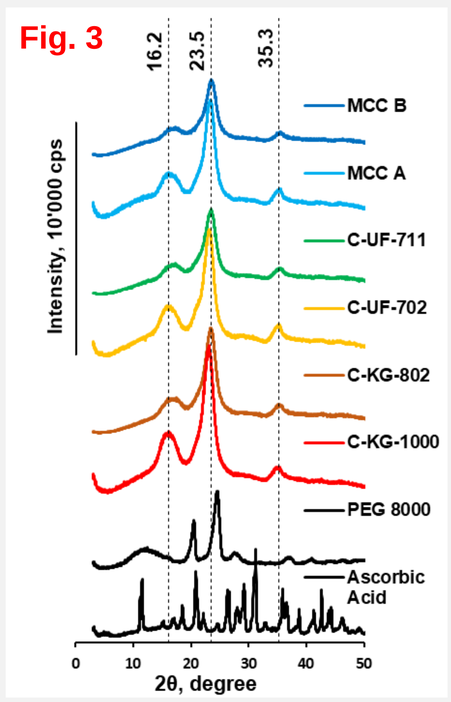
The dissolution test was carried out in USP II apparatus in 900 mL of 0.1 N HCl (pH 1.2) solution at 50 rpm paddle stirring speed at 37±0.5℃ (DIS 8000; Copley Scientific Ltd, England).

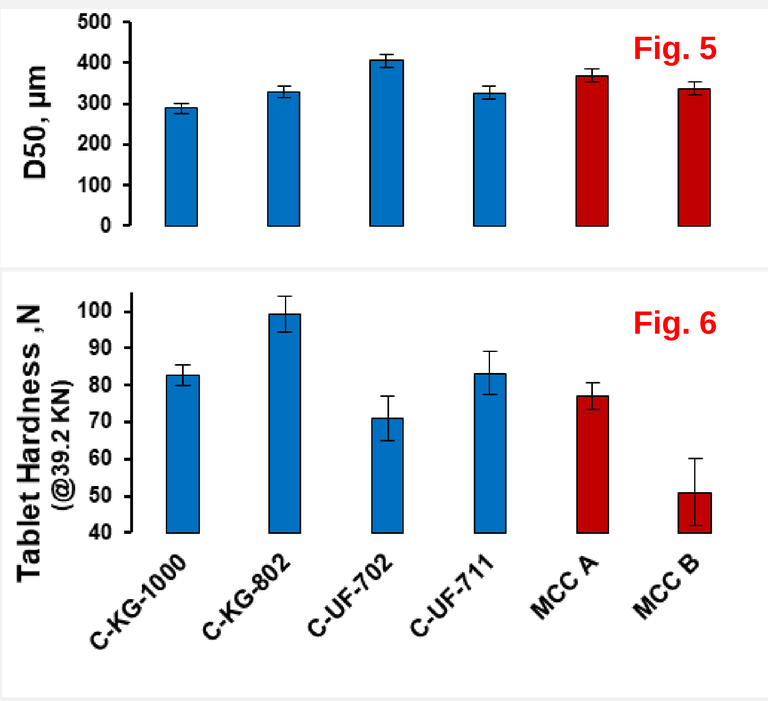
Table 1

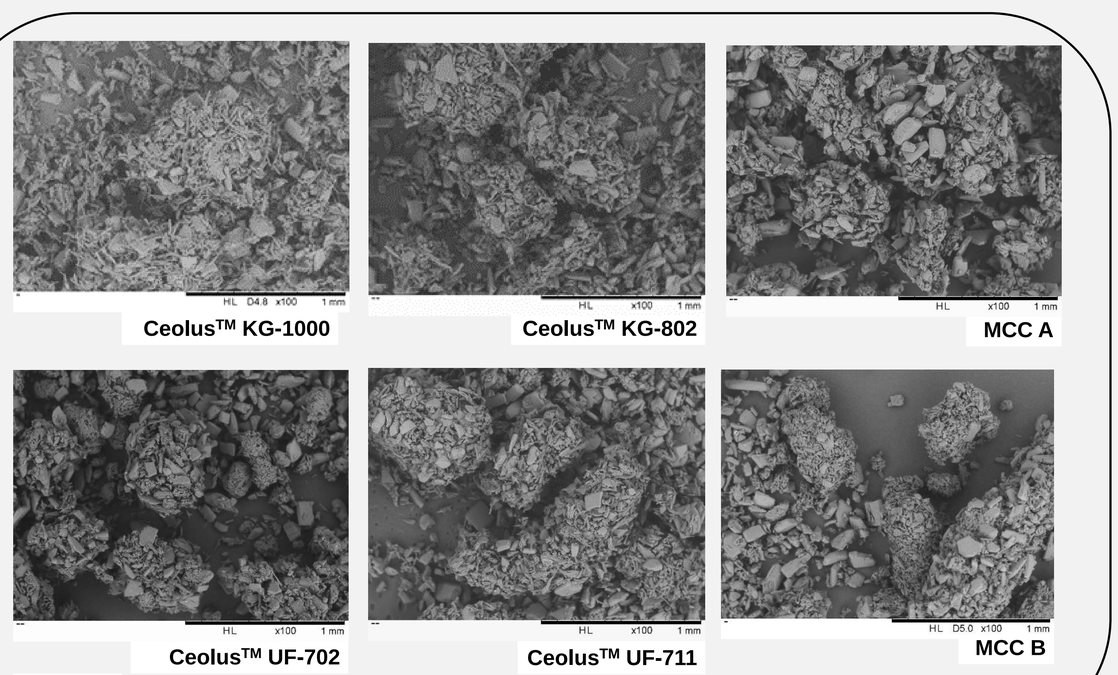
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
PEG 8000	15	15	15	15	15	15	15	15	15	15	15	15
Ascorbic acid	75	65	55	75	65	55	75	65	55	75	65	55
Ceolus™ KG-1000	10	20	30	–	–	–	–	–	–	–	–	–
Ceolus™ UF-702	–	–	–	10	20	30	–	–	–	–	–	–
MCC A	–	–	–	–	–	–	10	20	30	–	–	–
Ceolus™ UF-711	–	–	–	–	–	–	–	–	–	20	–	–
Ceolus™ KG-802	–	–	–	–	–	–	–	–	–	–	20	–
MCC B	–	–	–	–	–	–	–	–	–	–	–	20

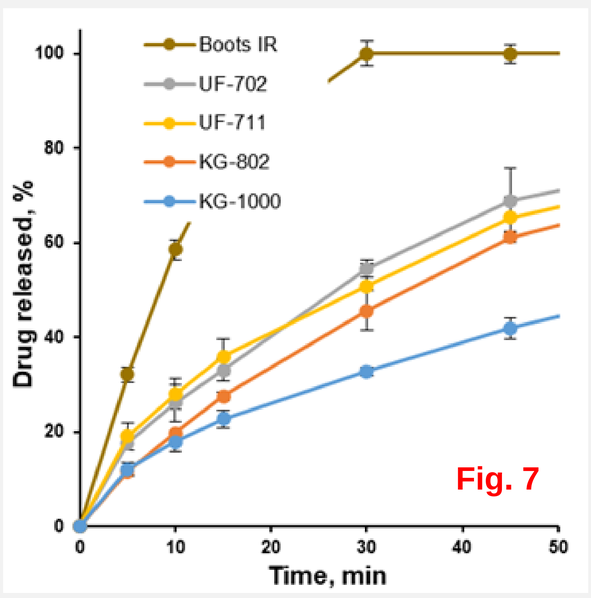


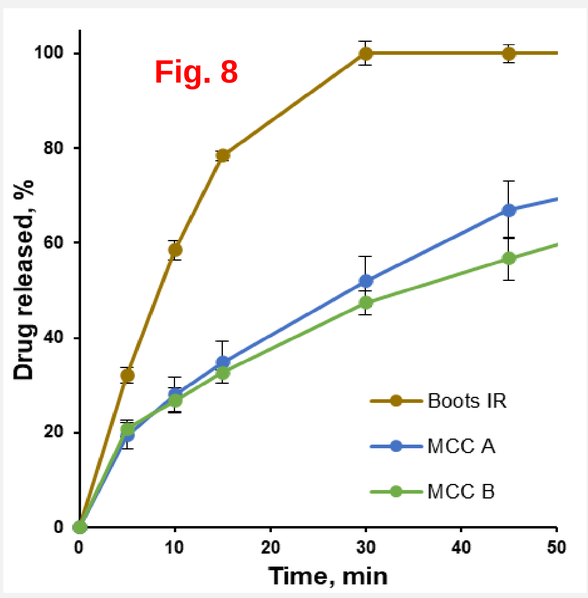












Results

- Ascorbic acid ($D_{50\%}$=85.9 µm) and PEG 8000 ($D_{50\%}$=467.3 µm) have shown thermal stability up to 200℃ (TGA; the data not presented). Ascorbic acid and PEG 8000 demonstrated Mp of 195.0 and 65.3℃, respectively (DSC; the data not presented).
- The solid-state of MCC powders was DSC (**Fig. 2**) and pXRD (**Fig. 3**) comparable.
- The solid-state ascorbic acid was not affected by twin-screw melt granulation based on DSC and pXRD results.
- For Ceolus™ KG-1000 (F1-3), UF-702 (F4-6) and MCC A (F7-9), the particle size of granules decreased along with MCC concentration increases from 10 to 30 % (the data not presented). That could be explained by increasing specific surface area of physical mixture and decreasing effective heat conductivity along with the increase of MCC concentration.
- At MCC content of 20% (F2, 5, 8 and F10-12), TSMG of formulations resulted in average particle size ($D_{50\%}$) of approx. 300-400 µm (**Fig. 4** and **Fig. 5**). And the highest average particle size was achieved for Ceolus™ UF-702.
- At MCC content of 20% (F2, 5, 8 and 10-12), the tablet hardness increased in the following sequence: MCC B < UF-702 < MCC A < KG-1000 < UF-711 and the highest tablet hardness was achieved for Ceolus™ KG-802 (**Fig. 6**).
- For Ceolus™ grades, the dissolution rate was increased in the following sequence KG-1000 < KG-802 < UF-711 ≈ UF-702 (**Fig. 7**). For MCC A and B grades, the dissolution from tablets with MCC A was faster than from tablets with MCC B (**Fig. 8**).
- For all formulations, the drug release rate was much slower than for market Boots IR tablets that could be easily increased by adding superdisintegrant.

Conclusion

- The effect of Ceolus™ KG-1000, KG-802, UF-711, UF-702 and MCC A and MCC B on the average particle size, tablet hardness and drug release from tablets of twin-screw melt granulated formulations was successfully investigated.
- At MCC content of 20%, all formulations demonstrated comparable average particle size of approx. 300-400 µm.
- While the highest tablet hardness was achieved for Ceolus™ KG-802.

Ref.: Horváth, Z.M., L. Petersone, and V. Mohylyuk, ***Twin-screw melt granulation with PEG 8000: Effect of binder particle size and processing temperature on the granule and tablet properties***. Adv Powder Technol, 2024. 35(9), DOI: 10.1016/j.apt.2024.104585.

Mohylyuk V, Ding Y, Shmyrova J, Andrews GP. Effect of Microcrystalline Cellulose (MCC) Grade on the Properties of Twin-Screw Melt Granulated Formulations of Ascorbic Acid. European Conference on Pharmaceutics 2025.03.24-25: Porto, Portugal.