# Twin-Screw Melt Granulation with PEG 8000: effect of binder particle size and processing temperature on the granule and tablet properties

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PBP WORLD MEETING

14th PBP World Meeting; Vienna, Austria, 2024, DOI: 10.13140/RG.2.2.16209.54883/1

## Introduction

- High-drug-loaded tablets and capsules are desirable and are manufactured using granulation as an additional step. Replacing batch wet granulation with twin-screw melt extruder as a continuous solventless process is gaining popularity. **PEG 8000** being one of the most popular excipients used for melt granulation lacks thorough investigation regarding its effect on the mechanical properties of tablets. Along with PEG 8000, a mixture of microcrystalline cellulose (**MCC**) and calcium phosphate anhydrous (**$CaHPO_4$**) was chosen for granulation due to its unsatisfactory flowability.

- **The aim of this study** was to investigate the effect of PEG 8000 particle size and twin-screw melt granulation temperature on the properties of resultant MCC-$CaHPO_4$ granules and their tablets.

## Materials

- **MCC** - CEOLUS UF-711 (Asahi Kasei, Japan); **$CaHPO_4$** - DI-CAFOS A60 (Budenheim KG, Germany); **PEG 8000** - Kollisolv® (BASF SE, Germany)
- Silica dioxide - SYLOID® 244FP (Grace GmbH, Germany) and Sodium stearyl fumarate - PRUV® (JRS Pharma, Germany) were used for directly compressed tablets (**DC**) where PEG 8000 was not used [ref.].

## Methods

- **Twin-Screw Melt Granulation** was carried out using a **Pharma 11** Extruder without nozzle, a Volumetric Mini Feeder, and a Conveyor (Thermo Electron CorporationGermany). The part of barrel that was used had a flighted length of 259 mm and a diameter of 11 mm with a length/diameter ratio (L/D) of 23.5:1. The screw design consisted of 1 L/D feed screw elements
- Tablets (Table 1; D 11.28 mm; flat punches; 500 mg) were prepared using a compaction simulator (**Styl'One Nano**, Medelpharm, France) simulating small rotary tablet press at 70 rpm; 50 MPa pre-compaction pressure and 100-250 MPa compaction pressure.
- The tablet thickness (t), diameter (d), and hardness (F), were measured (n=10) by a tablet tester (**ST50 WTDH**, SOTAX AG, Switzerland) immediately after the compaction and converted into tensile strength(MPa).
- The calculated true density of composition was obtained on the true density (ρt) of components and their shares (x, w/w):

$$\rho t = (\rho_{exc\,1} \cdot x_{exc\,1}) + (\rho_{exc\,2} \cdot x_{exc\,2}) + \cdots + (\rho_{exc\,i} \cdot x_{exc\,i})$$

- For in-die Heckel plot, the relative density ln**(1/ε)** was calculated with Alix software (Medelpharm). The relative density and compaction pressure (P,) data were plotted in accordance with the Heckel equation:

$$ln(1/\varepsilon) = \mathbf{MPa}K \cdot P + ln(1/\varepsilon 0) = K \cdot P + A$$

- **Optical** (BA410E, Motic, China); **Scanning Electron** (TM4000 Plus, Hitachi, Japan); **Raman** (Virsa™, Reinshaw plc., UK) **microscopy** were used.

**Table 1**

| | | S135 | M115 | M135 | M155 | B135 |
|---|---|---|---|---|---|---|
| Formulation | MCC (wt.%) | 56 | | | | |
| | $CaHPO_4$ (wt.%) | 34 | | | | |
| | PEG 8000 0-200 µm (wt.%) | 10 | - | - | - | - |
| | PEG 8000 200-400 µm (wt.%) | - | 10 | 10 | 10 | - |
| | PEG 8000 400-500 µm (wt.%) | - | - | - | - | 10 |
| Processing parameters | Zone 1 (°C) | 20 | | | | |
| | Zone 2 (°C) | 80 | 70 | 80 | 90 | 80 |
| | Zone 3 (°C) | **135** | **115** | **135** | **155** | **135** |
| | Zone 4 (°C) | **135** | **115** | **135** | **155** | **135** |
| | Zone 5 (°C) | 60 | 60 | 60 | 60 | 60 |
| | Feed rate (g/min) | 1.582 | | | | |
| | Screw speed (rpm) | 120 | | | | |
| | Torque (%) | 2 | | | | |

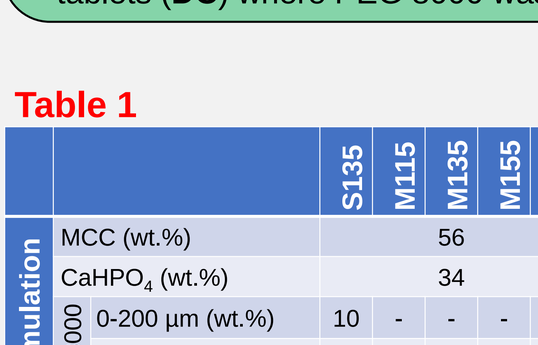
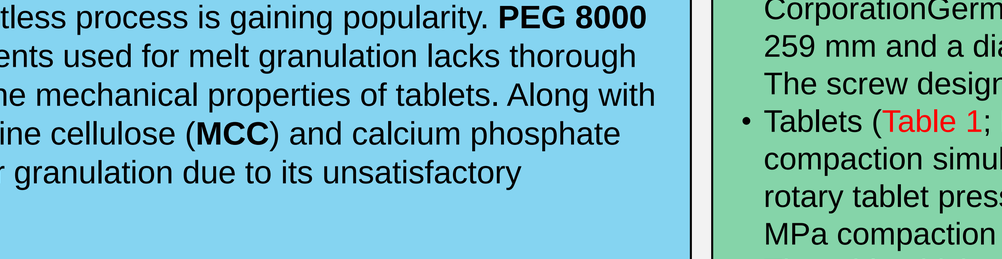



Fig. 1



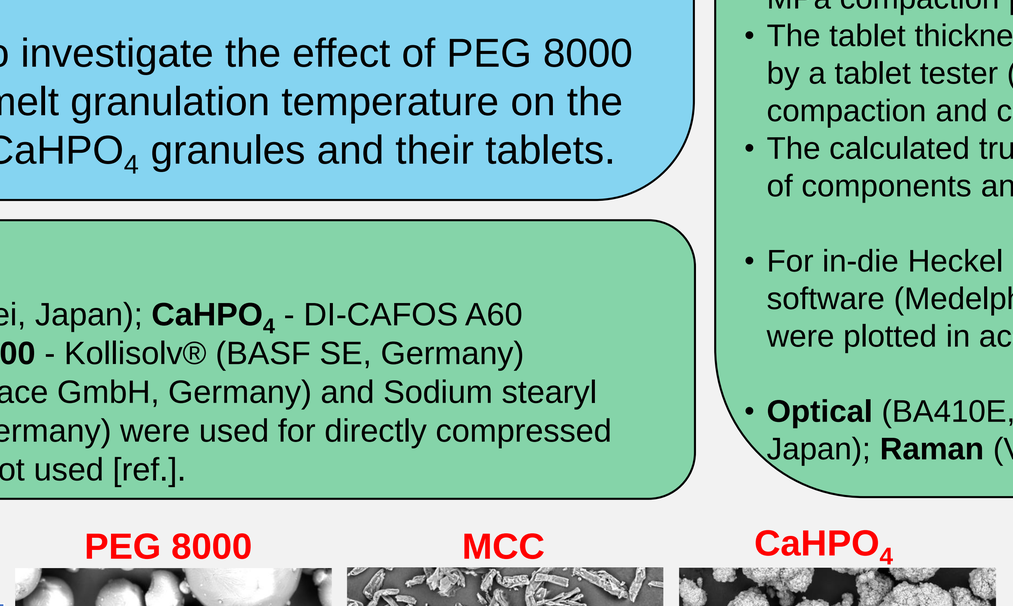




Fig. 2

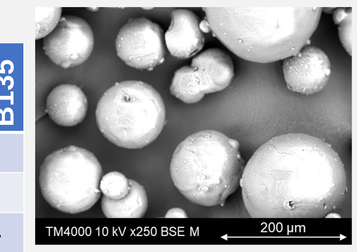



Fig. 3

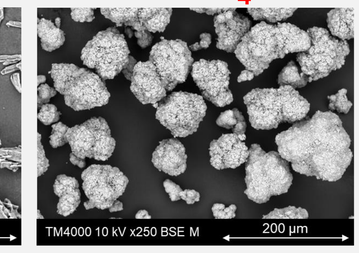



Fig. 4

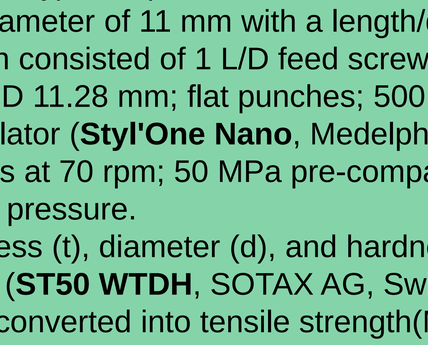



Fig. 5

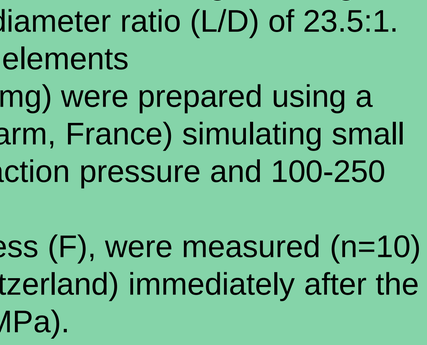



Fig. 6

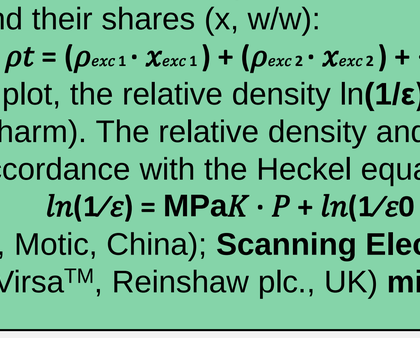



Fig. 7

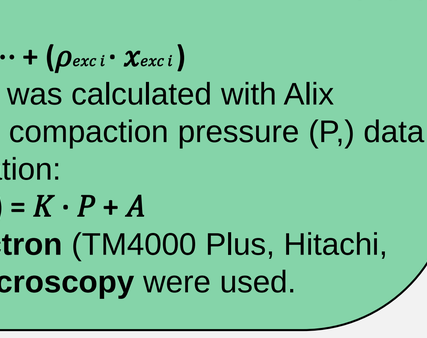



Fig. 8

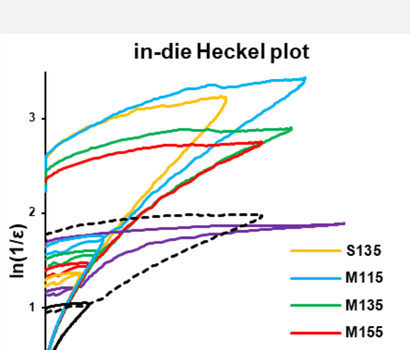



Fig. 9

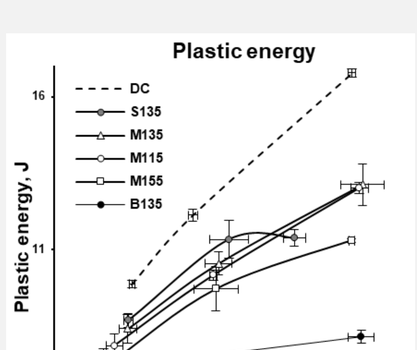



Fig. 10

## Results

- The size of granules increased with increasing PEG 8000 particle size and granulation temperature (**Fig. 1**)
- Optical microscopy of tablets revealed the individual granules and their points of contact (**Fig. 2**)
- Raman mapping (**Fig. 3**) confirmed the location of components and their conformation according to the optical microscope images in **Fig. 2**.
- $CaHPO_4$ particles are surrounded by PEG 8000 coated MCC particles within tablets (**Fig. 4**).
- The plasticity of formulations increased with decreasing PEG 8000 particle size and with decreasing granulation temperature (**Fig. 5**).
- The plastic energy (**Fig. 6**) and tensile strength (**Fig. 8**) of formulations (up to 150 MPa) decreased with increasing PEG 8000 particle size and with increasing granulation temperature.
- The elastic energy of formulations increased with increasing PEG 8000 particle size and granulation temperature (**Fig. 7**).
- Compressibility decreased with increasing PEG 8000 particle size and with increasing granulation temperature (**Fig. 9**).

## Discussion & Conclusion

- PEG 8000 particle size and granulation temperature influenced the granule's properties (**Fig. 1, 5-9**)
- Structure of granules influenced formulation plasticity (**Fig. 5**)
- Structure of granules, their plasticity, and structure of tablets influenced their mechanical properties (**Fig. 7-10**).
- Most plastic formulations showed best tabletability profiles (**Fig. 6, 8**).
- Melt-granulated formulations showed lower tensile strength compared to ungranulated directly compressed tablets (**Fig. 8**).

**Ref.:** Mohylyuk V, Paulausks A, Radzins O, Lauberte L. ***The Effect of Microcrystalline Cellulose–$CaHPO_4$ Mixtures in Different Volume Ratios on the Compaction and Structural–Mechanical Properties of Tablets***. Pharmaceutics. 2024;16(3), 10.3390/pharmaceutics16030362.

Horváth Z.M, Liga L, Mohylyuk V. Twin-Screw Melt Granulation with PEG 8000: effect of binder particle size and processing temperature on the granule and tablet properties.