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Evaluation of different mannitol grades in dry granulation process by roller compaction

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PURPOSE

Evaluate different commercial grades of mannitol to be used in dry granulation by roller compaction (RC), for comparing the compactability of dry granules obtained

Dry granulation by roller compaction:

- improves powder bulk density and flowability
- prevents segregation issues of highly potent drugs
- ideal for use with moisture and heat sensitive drugs
- benefits lower costs and smaller equipment footprint
- can be inserted in a continuous manufacturing system

Mannitol for oral formulation:

- high solubility
- pleasant organoleptic properties
- binder of choice in orally dispersible and chewable tablets
- available in several grades with different technological characteristics

METHODS

Materials: mannitol powder (Mannogem Powder, PO), spray dried (Mannogem EZ, SD and Mannogem XL, XL), granular (Mannogem granular, GR) and sodium stearyl fumarate (Lubripharm) were kindly donated by SPI Pharma, USA

- **Roller compactor** (TFC220, Freund Vector, IA, USA), screw feeder rotating at 20 rpm, knurled rolls 200mm diameter, 31 mm width, 2 rpm, compression force 15, 30 and 45 kN
- **Oscillating mill** (Oscillowit, Frewitt, CH) screen size 1.0 mm, square cross-section wire, 50 rpm
- **Specific surface area** (SSA) BET method (SA3100, BeckmanCoulter, I)
- **Particle size distribution** (PSD) digital image analysis (Qicpic, Sympatec, D)
- **Flow properties** according to USP-NF monograph (Stav 2003, J. Engelsmann, D)

  Compressibility Index = 100 x $[(V_o - V_t)/V_o]$
- **Morphology** by scanning electron microscopy (SEM, Leo1430, Carl Zeiss, CH)
- **Rotary tablet press** (AM8S, Officine Meccaniche Ronchi, I), flat punches, 11.28 mm diameter, compression force F_A 1-50 kN, 20 rpm, 400 mg, 0.5% lubricant blended for 2 min (Turbula mixer, WAB, CH)
- **Tensile strength** (TS according to Fell and Newton [3,4]. TBH30, Erweka, D, n=3). Height and diameter were measured by digital micrometer (Digital IDC, Mitutoyo, J)
- **Compactability** (CP) calculated by the slope of the regression line from the TS vs pressure profiles (95% i.c., multiplied by 10^5). Calculation of standard deviation of CP and statistics were performed according to Sonnergaard [4]

RESULTS

Raw materials characterization

Characterized for PSD, SSA, morphology bulk density, and flow properties, showed remarkable difference in physical properties

PO — fine, plate-shaped particles; passable-poorly flowable powder

SD and XL — moderately fine, spherical shaped particles with clear hollow/porous structure; good flow properties

GR — coarse, irregular and non-porous agglomerated particles; good flow properties

Dry granulation

All the materials could be successfully processed by RC

Proper size (>90% 500-1500 µm), increased bulk density and good/excellent flow properties could be obtained with all the material at each applied compaction pressure

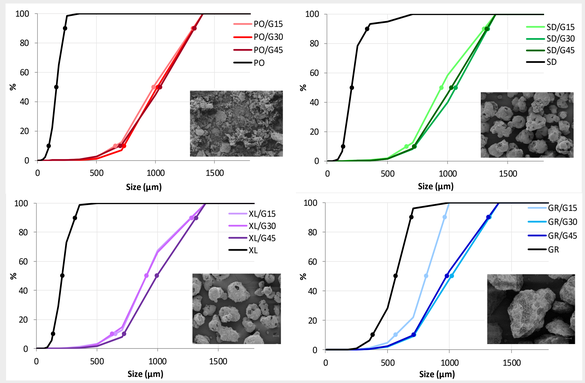
Granules showed higher SSA than the corresponding starting materials, thus indicating that particle fragmentation occurred under RC, which is typical of brittle materials [2]

Tableting

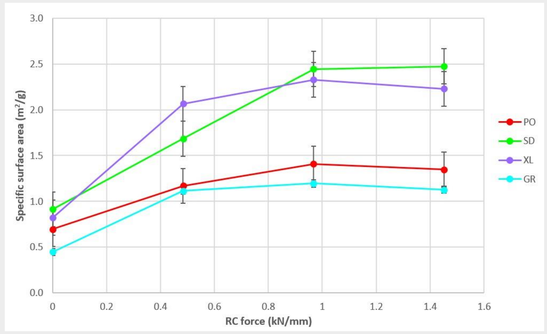
Dry granules could be compacted under forces up to approximately 400 MPa, producing tablets with increasing mechanical strength

Compactability after RC reduced for spray dried materials (SD and XL) as expected on the basis of the well-known phenomenon associated to particles enlargements and work-hardening [5]

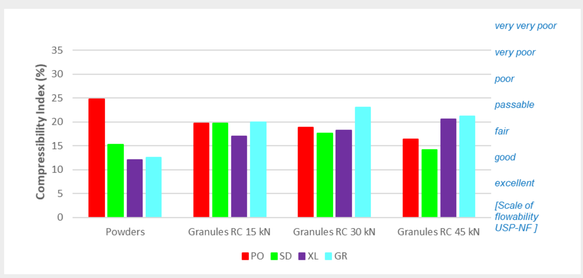
XL exhibited the highest CP values, even when processed with high RC pressure



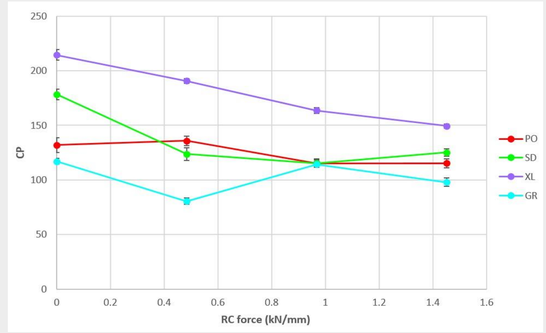
Particle size distribution of raw materials and granules roll compacted at different pressure and SEM pictures of PO, SD, GR and XL mannitol raw materials (magnification 500X)



Specific surface area profiles of mannitol PO, SD, XL and GR raw materials and granules obtained at different roller compaction pressure. Vertical bars represent standard deviation



Compressibility Index values of mannitol PO, SD, XL and GR raw materials and granules obtained at different roller compaction pressure



Compactability (CP) profiles of mannitol PO, SD, XL and GR raw materials and granules obtained at different roller compaction pressure. Vertical bars represent standard deviation of the slope

CONCLUSIONS

Various mannitol grades tested confirmed the ability to be used as filler in dry granulation process by roller compaction

Mannitol dry granules showed satisfactory technological properties in terms of flowability and bulk density while maintaining remarkable aptitude for enabling tableting process

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