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USE OF DIFFERENT MANNITOL GRADES TO IMPROVE THE FLOW AND TABLETING PROPERTIES OF POWDER MIXTURES DRY GRANULATED BY ROLLER COMPACTION

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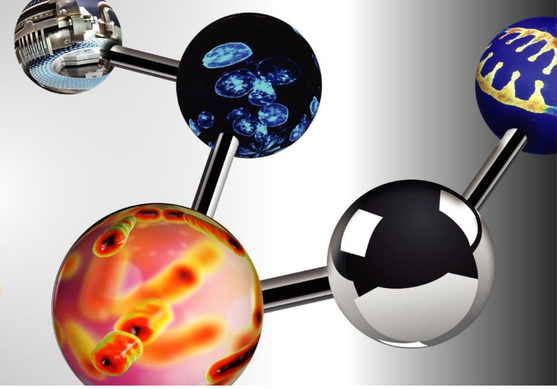

PURPOSE

- Dry granulation is widely used for the improvement of bulk density and flowability of powder blends or for the prevention of segregation of powder mixtures
- Paracetamol fine powder is notoriously known for its poor flowability properties, and in particular monoclinic form has been studied as the ideal model drug for exhibiting tableting issues (low crushing strengths and capping)
- Mannitol is a polyol extensively used in pharmaceutical formulations for its high solubility and pleasant organoleptic properties, which make it the diluent of choice for obtaining orally dispersible and chewable tablets

OBJECTIVE

The evaluation of the tableting properties of granulates obtained by roller compaction (RC) of binary mixtures prepared with different contents of paracetamol fine powder and using different commercial types of mannitol

METHODS

- **Materials:** Paracetamol fine powder (AC, Rhodapap Powder Ph.Eur., Novacyl Pharmaceutical, China). Mannitol powder (Mannogem Powder, PO), spray dried (Mannogem EZ and Mannogem XL, SPI, USA) and sodium stearyl fumarate (Lubripharm, LF, SPI, USA).
- **Powder mixing (**1 kg batch size, bin tumbler (4.5 l, Cyclops, VIMA, IT) containing 20, 40, 60, 80% paracetamol.
- **Roller compactor** (TFC220, Freund Vector, IA, USA), screw feeder rotating at 20 rpm, knurled rolls 200 mm 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
- **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 $[(V_0 - V_f)/V_0]$
- **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 std dev. of CP and statistics were performed according to Sonnergaard [4]

RESULTS

Granulation by roller compaction

- All powder materials and blends could be successfully dry-granulated
- Paracetamol powder, caused difficulties in consistent feeding of the rolls, due to its poor flowability

Characterization of granules

- Granules with proper size (90% 500-1500 µm) and increased bulk density were obtained in all cases
- Flow properties of granules were progressively compromised by the increasing content of paracetamol
- Granules obtained at higher RC forces generally resulted with better flowability
- Spray-dried mannitols showed a worsening in flowability after to RC process
- Granules prepared with mixtures containing paracetamol and mannitol EZ or XL produced the strongest tablets even if compactability after RC resulted reduced compared to powder mixtures
- Spray-dried materials under RC lost their porous structure causing the well-known phenomenon associated to particles enlargements and work-hardening
- With powder mixtures and granules containing mannitol EZ and XL it was only possible to obtain tablets up to 40% drug content. When employing higher RC forces (30 and 45 kN), mannitol PO allowed to prepare relatively softer tablets, but up to 80% drug content

Formulation code	Paracetamol (%)	Mannitol EZ (%)	Mannitol XL (%)	Mannitol PO (%)
EZ	0	100	-	-
AC20EZ80	20	80	-	-
AC40EZ60	40	60	-	-
AC60EZ40	60	40	-	-
AC80EZ20	80	20	-	-
XL	0	-	100	-
AC20XL80	20	-	80	-
AC40XL60	40	-	60	-
AC60XL40	60	-	40	-
AC80XL20	80	-	20	-
PO	0	-	-	100
AC20PO80	20	-	-	80
AC40PO60	40	-	-	60
AC60PO40	60	-	-	40
AC80PO20	80	-	-	20
AC	100	-	-	-

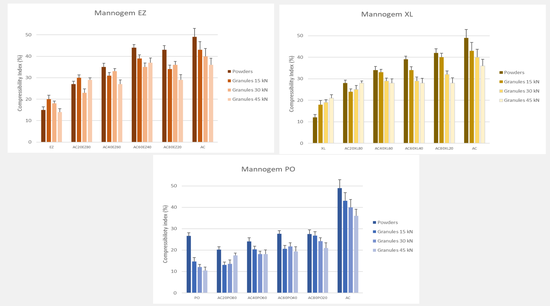

Figure 1. Compressibility index values of raw materials, powder blends and granules obtained at different RC force, using different mannitol/paracetamol ratios and different mannitol grades (n=3). Vertical bars represent standard deviation.

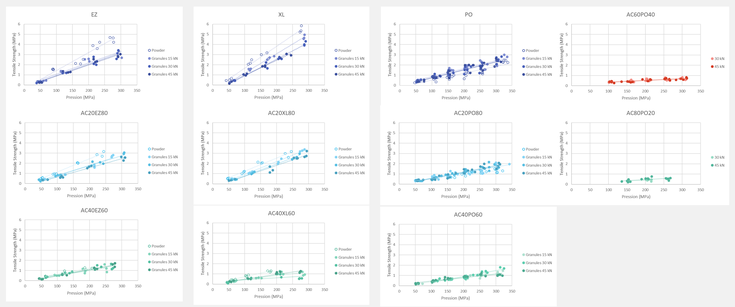

Figure 2. Tensile strength vs pressure profiles of powder blends and granules obtained at different roll compression forces using mannitol EZ, XL and PO and increasing content of paracetamol.

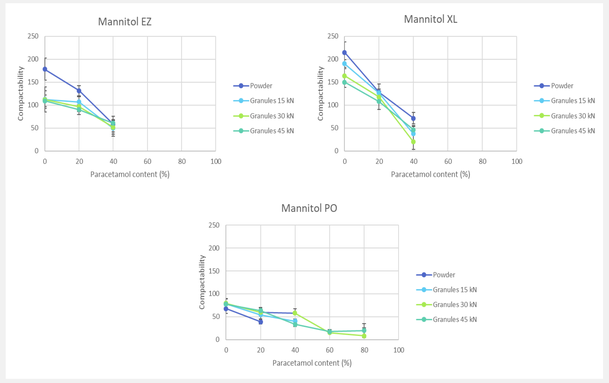

Figure 3. Ability to compaction of mannitol EZ, XL and PO and blends with different paracetamol content RC at different roller compaction forces

CONCLUSIONS

- **Dry granulation by RC confirmed the possibility of enhancing the bulk density and flowability properties of critical powder blends**
- **The use of powdered mannitol demonstrated the ability to prepare tablets with high drug loading up to 80% when dry granulation was operated at higher RC force**

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