FORMATION OF DELTA-MANNITOL BY CO-SPRAY DRYING

ENHANCING TABLETABILITY OF PARACETAMOL-MANNITOL FORMULATIONS

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Introduction

Mannitol (MAN) is a polymorphic excipient (α-, β-, δ-MAN) commonly used in tablets. Delta-mannitol (δ-MAN) has the best compaction behaviour, but reproducible and scalable production is challenging.

Paracetamol (PCM), a common analgetic and antipyretic, is hard to tablet in high-dosed formulations due to capping.

Objectives

→ Improve compressibility and tabletability of paracetamol-mannitol (PCM-MAN) formulations by the formation of δ-MAN by co-spray drying.

Materials and Methods

Spray dryers:
- 4M8-Trix (ProCepT, Belgium): lab-scale
- Mobile Minor (Gea NIRO, Germany): pilot-scale

Starting materials:
- PCM micronized (Malinckrodt, USA)
- β- MAN: Pearlitol 50C (Roquette, France)
- Polysorbate 80 (Sigma-Aldrich, USA)

Influence of formulation characteristics

Design of Experiments (DOE) on 4M8-Trix:
- PCM-MAN ratio varied between 1:99 and 70:30 (w/w),
- Solids load varied between 2 and 40% w/w
- Constant process parameters

Parameter	4M8-Trix
Airflow (m³/min)	0.25
Temp. In (°C)	160
Nozzle air (L/min)	7.5
Feed rate (g/min)	2.5
2-fluid nozzle tip (mm)	1

Table 1: Process parameters formulation DOE 4M8-Trix

Influence of process parameters

DOE on 4M8-Trix and Mobile Minor:
- Formulation: PCM-MAN 30:70, 20% w/w, Tween 80 0.1% w/w

Parameter	4M8-Trix	Mobile Minor
Airflow (m³/min)	0.25 – 0. 60	0.60 – 1.00
Temp. In (°C)	160 – 200	180 – 200
Nozzle air (L/min)	5 – 12	90 – 200
Feed rate (g/min)	2.5	20
2-fluid nozzle tip (mm)	1	2

Table 2: Process parameters DOE 4M8-trix and Mobile Minor

Data analysis with MODDE (Umetrics, Sweden) software

Evaluation of co-spray dried powders

RxN2 Raman spectrometer (Kaiser, USA)
- Data analysis with SIMCA (Umetrics, Sweden) software
- Qualitative determination of % δ-mannitol via ratio model

Tabletability

Styl'One Compaction simulator (Medelpharm, France)
- Tablet weight: 500 mg
- Compaction force: 50 – 100 – 150 – 200 – 250 – 300 MPa
- + 2 % Magnesium Stearate

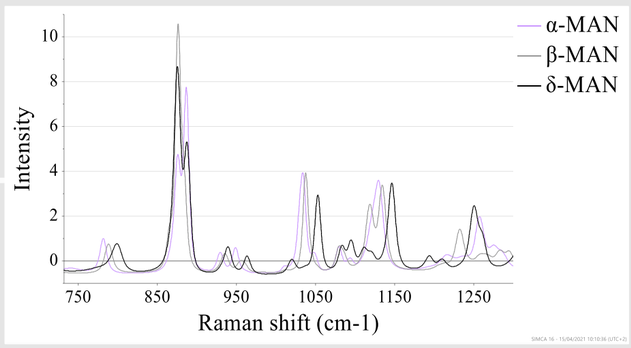

Fig. 1: Raman spectra of the MAN polymorphs (α, β, δ)

Fig. 2: 4M8-Trix (left) and Mobile Minor (right) spray dryers

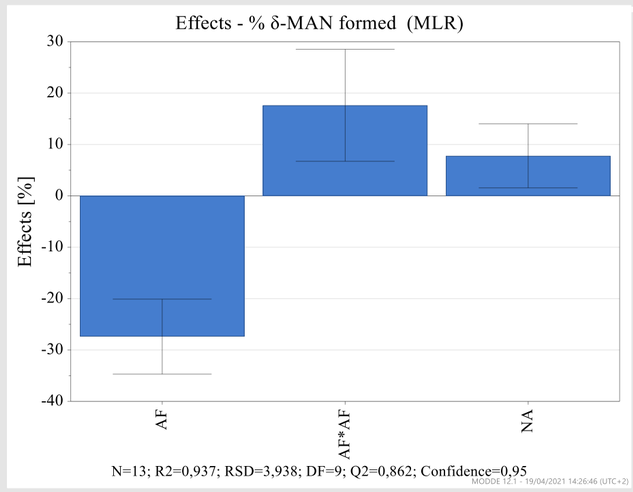

Fig. 3: Effect plot influence process parameters on δ-MAN formation

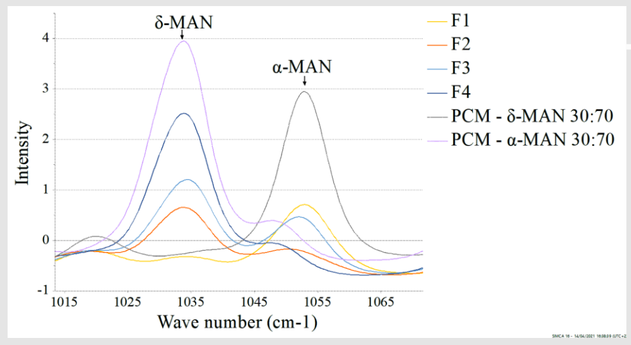

Fig. 4: Raman spectra selected samples and references

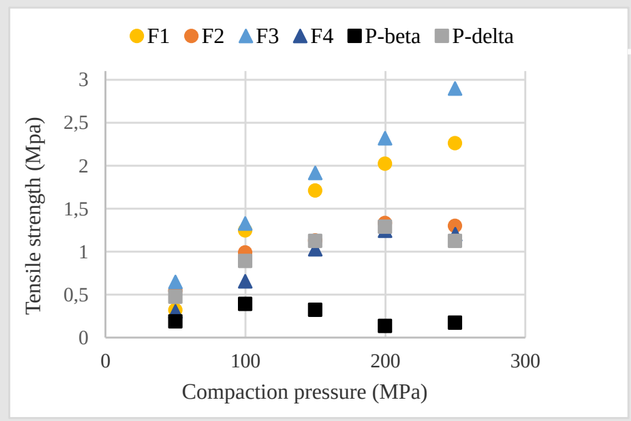

Fig. 5: Tensile strength of the selected sample- and reference tablets

Acknowledgements

ProCepT and Xedev are acknowledged for their contribution to the study and the use of their 4M8-Trix lab-scale spray dryer.

Physical mixtures tableted as reference formulations:
- PCM – β-MAN 30:70 (P-beta)
- PCM – δ-MAN 30:70 (P-delta)
- + 2 % Magnesium Stearate

Results and Discussion

Formation of δ-MAN

Influence of formulation characteristics (PCM-MAN ratio, solids fraction %w/w):

→ δ-MAN was always formed:
- Next to β-MAN for low PCM-MAN ratios (25 – 35% δ-MAN)
- Next to α-MAN for high PCM-MAN ratios (35 – 55% δ-MAN)

Influence of process parameters:

→ Airflow has the most pronounced impact on δ-MAN formation: Airflow is inversely proportional to the formation of δ-MAN and directly proportional to the formation of α-MAN.

→ Other process parameters have a smaller impact:
- Nozzle air is directly proportional to the formation δ-MAN (more pronounced for low airflow)
- Inlet temperature appeared a non-significant model term

→ These effects were observed for both the 4M8-Trix and the Mobile Minor spray dryer.

→ Even at higher airflows a small amount of δ-MAN was formed.

→ The starting material (β-MAN) was via Raman spectrometry no longer detectable. This is consistent with the previous results, where for higher PCM-MAN ratios δ-MAN was found next to α-MAN.

→ Selection of 4 samples for tabletting

Formulation: PCM-MAN 30:70, 20% w/w, Tween 80 0.1% w/w

Code	Airflow (m³/min)	Temp. In (°C)	Nozzle Air (L/min)	Spray dryer	% δ-MAN
F1	0.25	160	7.5	4M8-Trix	44
F2	0.43	160	7.5	4M8-Trix	25
F3	0.63	180	154	Mobile Minor	33
F4	0.74	180	154	Mobile Minor	25

Table 3: Selected samples for tabletting

Tensile strength

- Tablets with δ-MAN (P-delta) were stronger than tablets with β-MAN (P-beta).
- Tablets from co-spray dried powders were at least as strong or stronger than tablets made from P-delta.
- F3 had a superior tabletability, although F1 contained the highest amount of delta-mannitol. This could be due to differences in particle size.

Stability

Raman spectra after 1, 3, 6, 9 months showed that the amount of δ-MAN remained stable.

Conclusion

It is possible to create PCM-MAN powders with better tabletability properties by co-spray drying. Stronger tablets are achieved because of the formation of delta-mannitol, as well as by the effect of co-processing.

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