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FORMATION OF DELTA-MANNITOL BY CO-SPRAY DRYING: ENHANCING THE TABLETABILITY OF PARACETAMOL/MANNITOL FORMULATIONS

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Abstract

δ-mannitol is a metastable polymorph of mannitol, known for its superior tableting properties. However, there is no easy, reproducible and scalable production method for δ-mannitol. It was evaluated whether δ-mannitol could be formed via co-spray drying with an API exhibiting tabletability issues, to improve the API tabletability in a one-step process prior to compaction. Aqueous suspensions with paracetamol and β-mannitol were co-spray dried. Raman spectroscopy was used to identify the mannitol polymorphs. In these formulations, paracetamol was the key factor to allow the formation of δ-mannitol since no traces of the δ-polymorph could be detected after spray drying a pure mannitol feed. The presence of δ-mannitol after co-spray drying was confirmed even for low paracetamol/mannitol ratios (1:99). The δ-mannitol content varied depending on the process drying parameters, predominantly by the airflow. A lower airflow promoted the formation of δ-mannitol, while more α-mannitol was formed when applying a higher airflow. The starting material, β-mannitol, was often no longer detectable by Raman spectroscopy. The tabletability of the spray dried powders clearly improved in association with the δ-mannitol concentration. The co-processed powders showed superior tabletability in comparison with physical mixtures of the starting materials. Harder tablets with a maximal tensile strength of 2.9 MPa at a main compression pressure of 247 MPa were achieved.

Key Words

Delta mannitol

Spray drying

Coprocessing

Direct compression

Paracetamol

Tabletability

Abbreviations

CTC	Compressibility, Tabletability and Compactability
d50	Median particle size
DOE	Design of Experiments
HPMC	Hydroxypropyl methylcellulose
MAN	Mannitol
MD	Maltodextrin
PCM	Paracetamol
PVP	Polyvinylpyrrolidone
SEM	Scanning electron microscopy
TS	Tensile strength

1. Introduction

Tablets have been the most widely used dosage form in the pharmaceutical industry for decades, considering their ease of manufacturing, accurate dosing and convenient administration. They exhibit excellent stability in comparison with liquids and are stronger and more resistant to external stress than capsules [1,2].

Mannitol is a polymorphic acyclic sugar alcohol commonly used as excipient in tablets because of its non-hygroscopic properties and low drug-interaction potential [3]. It is also often used in chewable and orodispersible tablets for its cooling effect and rapid disintegration, respectively. Numerous polymorphic forms with various nomenclatures were reported in literature, creating a confusing picture. Burger *et al*. [4] provided a clear overview of these different polymorphs and confirmed the existence of three pure polymorphic forms. They are referred to as modification I, II and III, or β-, α- and δ-mannitol, respectively, in agreement with the Walter-Levy nomenclature [5,6]. β-mannitol is the thermodynamically stable form. α- and δ-mannitol are proven metastable at 25 °C over a period of at least 5 years [4,7,8].

Of all polymorphs, δ-mannitol is widely described to have the best compaction behavior, followed by α- and β-mannitol [3,4]. This may be related to its different crystal form. α- and β-mannitol are identified as orthorhombic crystals, whereas δ-mannitol is monoclinic. Crystallization procedures to form δ-mannitol are described in literature [9], but reproducible and scalable production of δ-mannitol is challenging [4]. Commercially available mannitol products consist mostly of β-mannitol, or a mixture of α- and β-mannitol for spray dried grades [5]. Alternatively, δ-mannitol can be obtained via freeze drying or co-spray drying [10,11]. Co-spray drying has been gaining popularity over the years and is widely used to produce directly compressible excipients, for example Cellactose® [1,2]. It has previously been described in literature that it is possible to obtain δ-mannitol via co-spray drying. Hulse *et al*. [12] described the formation of δ-mannitol after co-spray drying with trypsin and Vanhoorne *et al.* [13,14] investigated the effect of polyvinylpyrrolidone (PVP) on the formation of δ-mannitol during co-spray drying. In the latter research, aqueous solutions of mannitol and PVP were spray dried on a pilot-scale spray dryer, resulting in the formation of δ-mannitol. Simultaneously, paracetamol crystals were introduced in the drying chamber via a specific set-up. These drug particles were successfully coated with a mannitol-PVP layer, and exhibited a superior tabletability compared to physical mixtures of the starting materials [14]. In the current study, a different approach to obtain paracetamol/mannitol powders with improved tableting properties was investigated by directly co-spray drying a suspension containing paracetamol and β-mannitol in a predefined ratio, thus using a regular spray drying set-up. In this research it was evaluated under which conditions δ-mannitol could be formed and if it was possible to improve the compaction properties of paracetamol/mannitol formulations by co-spray

drying in one preparatory step. The effects of formulation characteristics as well as process parameters on the formation of δ-mannitol were considered. The co-spray dried powders were evaluated via Raman spectroscopy and quantified using a ratio model prior to tableting on a compaction simulator.

2. Materials and methods

2.1. Materials

A commercially available grade of β-mannitol (Pearlitol 50 C) by Roquette (Lestrem, France) and micronized monoclinic paracetamol by Malinckrodt Chemical (Hazelwood, USA) were used as starting materials. Distilled water was used to prepare the suspensions. Polysorbate 80 by Sigma-Aldrich (Missouri, USA) was used as stabilizer for the suspensions. δ-mannitol (Parteck Delta-M) was kindly donated by Merck (Darmstadt, Germany) as a reference material. A reference sample of α-mannitol was prepared by melt crystallization [9]. Maltodextrin (MD) (C*Dry MD, Cargill, Wayzata, USA) and hydroxypropyl methylcellulose (HPMC) (Methocel E5 Premium LV, Dow Chemical, Midland, USA) are commonly used binders in tablet formulations and were used as stabilizer in the suspensions used for spray drying. Magnesium stearate (Fagron, Waregem, Belgium) was used as lubricant during tableting.

2.2. Methods

2.2.1. Formation of α-mannitol

α-mannitol was prepared via melt crystallization as described by Cornel *et al*. [9]. 15 g of β-mannitol was heated to 170°C to form a melt. Afterwards the melt was cooled to room temperature to form α-mannitol crystals. After collection the crystals were ground, sieved <125 µm and stored at room temperature.

2.2.2. Preparation of the feed suspensions

The feed suspensions were stirred for 2 hours on a magnetic stirrer at room temperature to assure steady state stability.

2.2.3. Co-spray drying

Experiments were conducted on a 4M8-TriX lab-scale spray dryer (Procept, Zele, Belgium) and a Mobile Minor pilot-scale spray dryer (GEA Niro, Copenhagen, Denmark) to study the δ-mannitol formation on different scales and at different drying conditions, i.e., laminar airflow on the 4M8-TriX vs. turbulent airflow on the Mobile Minor. Both spray dryers operated in co-current mode and were equipped with a bi-fluid nozzle (nozzle orifice 1 mm). The 4M8-TriX was operated in its extended setup and was equipped with a 12-roller peristaltic pump and Tygon® MHLL tubing (internal diameter 1.14 mm). An external Watson-Marlow peristaltic pump (520U, Watson Marlow, Cornwall, UK) with marprene tubing (internal diameter 4.8 mm) was used to feed the suspensions to the Mobile Minor. The length of the

tubing and the distance between the pump and the nozzle were kept as short as possible. The suspensions were continuously stirred while being fed.

2.2.3.1. Preliminary experiments

To investigate whether δ-mannitol can also be formed after spray drying a pure mannitol feed, a mannitol solution (10% w/w total solids content) and suspension (40% w/w total solids content, + 0.1% w/w polysorbate 80) were prepared with Pearlitol 50 C. The experiments were performed on a 4M8-TriX lab-scale spray dryer using fixed process conditions: airflow 0.25 m^3/min, inlet temperature 160°C, nozzle atomization gas 7.5 L/min and feed rate 2.5 g/min. These process conditions were selected based on the results of in-house experiments that theoretically favor the formation of δ-mannitol.

2.2.3.2. Influence of the formulation on the formation of δ-mannitol

In the first set of experiments the influence of the formulation composition on the formation of δ-mannitol was investigated. A design of experiments (DOE) was used, applying a full factorial design with two variables at two levels (4 experiments and 3 center points, N1-N7). The paracetamol/mannitol (PCM-MAN) ratio (1:99-70:30 w/w) and the total solids content (2-40% w/w) were altered (Table 1). The total solids content is defined as the percentage of total solids initially present in the formulation. The suspended fraction is defined as the percentage of solids that remains in a suspension at steady state conditions. The suspended fraction ranged between 8 and 37% w/w for the suspensions listed in Table 1. Polysorbate 80 (0.1% w/w) was added as a stabilizer to the suspensions. As preliminary tests revealed no difference in polymorphic behavior of mannitol after spray drying with or without polysorbate 80, the stabilizer was considered a neutral formulation factor. The main outcome of the DOE was whether δ-mannitol could be formed under these conditions. The experiments were carried out on a 4M8-TriX lab-scale spray dryer using fixed process parameters. The airflow was set at 0.25 m^3/min, inlet temperature at 160°C, nozzle atomization gas at 7.5 L/min and feed rate at 2.5 g/min. These process conditions were selected based on the results of in-house experiments that theoretically favor the formation of δ-mannitol. The results were analyzed with Modde 12.1 (Umetrics, Umeå, Sweden) software.

Table 1. Overview of the formulation experiments.

Code	Ratio PCM:MAN (w/w)	Total solids content (% w/w)	Suspended fraction (% w/w)
N1	1:99	2	0
N2	1:99	40	35
N3	70:30	2	0
N4	70:30	40	37
N5, N6, N7	35.5:64.5	21	8

142 *2.2.3.3. Influence of process parameters on the formation of δ-mannitol*

143 In the second set of experiments the influence of process parameters on the formation of δ-mannitol
144 was investigated. All experiments were conducted with the PCM–MAN 30:70 formulation having a 20%
145 w/w total solids content and containing 0.1% w/w polysorbate 80. Using the 4M8-TriX, a Taguchi L18
146 fractional factorial design was applied with one variable at two levels and two variables at three levels
147 and (18 experiments and 3 center points, P1-P21). Airflow and nozzle atomization gas were varied at
148 three levels, the inlet temperature was varied at two levels and the feed rate was kept constant at 2.5
149 g/min. (Table 2). Considering that airflow and nozzle atomization gas were expected to have a notable
150 impact on the outcome, these parameters were varied at three levels in such a way that they cover
151 almost the entire experimental range of the equipment. As this was not feasible for the inlet
152 temperature, respecting the limits of the equipment and the required drying conditions for aqueous
153 formulations, the inlet temperature was only varied at two levels. The results were analyzed with
154 Modde 12.1 (Umetrics, Umeå, Sweden) software.

155 **Table 2.** Process parameter ranges for the DOE on the 4M8-TriX.

Parameters 4M8-TriX	Min.	Max.
Airflow (m^3/min)	0.25	0.60
Inlet temperature (°C)	160	200
Nozzle atomization gas (L/min)	5	12.5
Feed rate (g/min)	2.5	

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157 Subsequently, a limited number of experiments was performed on the Mobile Minor to verify the
158 trends seen on the lab-scale spray dryer. Based on the results of the experiments on the 4M8-TriX it
159 was decided not to carry out a full DOE on the Mobile Minor, but to make a careful selection of
160 experiments instead. Airflow, inlet temperature and nozzle atomization gas were varied, while the
161 feed rate was kept constant at 20 g/min (Table 3).

162 **Table 3.** Process parameter experiments on the Mobile Minor.

Code	Airflow (m^3/min)	Nozzle atomization gas (L/min)	Inlet temperature (°C)
G1	0.63	154	180
G2	0.63	200	180
G3	0.63	154	200
G4	0.71	154	180
G5	0.84	154	180
G6	1.03	154	180

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2.2.3.4. Influence of binders on the formation of δ-mannitol

Maltodextrin (MD) and hydroxypropyl methylcellulose (HPMC) are commonly used binders for tableting. It was investigated whether co-spray drying with the binders affected the formation of δ-mannitol. The suspensions had a total solids content of 20% w/w, and the paracetamol/excipients ratio was 30:70 w/w. The excipients fraction consisted of β-mannitol in combination with MD or HPMC (Table 4). No polysorbate 80 was used, since MD and HPMC acted as stabilizer. All experiments were executed under constant process conditions on the 4M8-Trix spray dryer. The airflow was set at 0.25 m^3/min, inlet temperature at 160°C, nozzle atomization gas at 7.5 L/min and feed rate at 2.5 g/min. These process conditions were selected based on the results of in-house experiments that theoretically favor the formation of δ-mannitol.

Table 4. Overview of the binder experiments.

Code	PCM (%)	MAN (%)	MD (%)		PCM (%)	MAN (%)	HPMC (%)
M1	30	60	10	H1	30	69	1
M2	30	50	20	H2	30	67	3
M3	30	40	30	H3	30	65	5

2.2.4. Preparation of physical mixtures

Physical mixtures of paracetamol and β- or δ-mannitol (PCM-MAN 30:70) were prepared via mixing in a tumbling blender (Turbula T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 5 min at 30 rpm. The reference mixtures were used to evaluate the potential of δ-mannitol and the possible benefits of coprocessing via spray drying on tabletability.

2.2.5. Preparation of tablets

Prior to tableting, the spray dried powders and the physical mixtures were blended with 2% magnesium stearate in a Turbula T2F tumbling blender for 3 minutes at 23 rpm to avoid excessive ejection forces. Tablets were produced on a STYL'One Evolution compaction simulator (Medelpharm, Beynost, France) equipped with cylindrical flat-faced Euro B punches of 11.28 mm diameter (Natoli Engineering Company, Saint Charles, MO, USA). The dwell time was 10 – 20 ms. Feeding was done manually to ensure reproducible tablet weight. Tablets of 500 mg (n = 10) were prepared at main compression forces of 54 (± 12), 105 (± 18), 153 (± 22), 201 (± 21) and 247 (±23) MPa.

2.2.6. Characterization of the co-spray dried powders

2.2.6.1. Raman spectroscopy

Raman spectra of the powders were recorded on a Rxn2 spectrometer (Kaiser Optical Systems - Endress+Hauser, Reinach, Switzerland). The Rxn2 was equipped with a fiber-optic PhAT probe and CCD detector. The laser wavelength was 785 nm with a laser power of 395 mW. The spectral range of the system was 400-1530 cm^{-1} with a resolution of 5 cm^{-1}. The analyzed spectral region to distinguish between the mannitol polymorphs was 840-1180 cm^{-1}. Spectra of each sample were recorded in threefold. Simca 16 software (Umetrics, Umeå, Sweden) was used to process the data. Standard Normal Variate pre-processing was applied to avoid baseline and physical variations due to sample placement.

2.2.6.2. Content uniformity

The paracetamol concentration in the spray dried samples was quantified by UV-VIS spectroscopy. Measurements were executed on a Shimadzu UV-1650 PC (Shimadzu, Kyoto, Japan). First, a calibration curve ranging from 25 to 100 µg/mL paracetamol was prepared by diluting a 1 mg/mL stock solution of paracetamol to the desired concentrations and measuring the absorbance at 290 nm in quartz cuvettes. Next, a precisely measured amount of spray dried sample was dissolved in distilled water and appropriately diluted according to the theoretical paracetamol concentration in the formulation. All measurements were executed in triplicate. A paracetamol concentration in the [90-110 %] interval of the theoretical concentration was considered acceptable.

2.2.6.3. Loss on drying

The residual moisture content was determined via loss on drying using a HC 103 Moisture Analyzer (Mettler Toledo, Zaventem, Belgium). Powder samples of 500 mg were placed in the oven on an aluminum weighing dish (Heathrow Scientific, Nottingham, United Kingdom) and heated to 105°C. Weight loss due to water evaporation was monitored until a stable weight (switch-off criterion: < 3 mg weight change per 50 s) was obtained.

2.2.6.4. Morphology

The starting materials and samples were visually evaluated by scanning electron microscopy (SEM) using Phenom Pro Suite (Phenom – Thermo Fisher Scientific, Waltham, Massachusetts, USA). Samples were prepared by distributing a small amount of powder evenly on the conductive carbon tab of the sample holder, followed by sputtering with a gold coating (Quorum, Laughton, United Kingdom).

2.2.6.5. Particle size analysis

Laser diffraction was used to evaluate the particle size distribution of both the spray dried powders and the starting materials. Measurements were carried out on a Mastersizer S long bench version (Malvern Instruments, Worcestershire, United Kingdom) equipped with the Malvern 300 lens. The dry

measuring method was applied. The mean volume diameters were calculated via the Mastersizer 2000 software.

2.2.6.6. Flowability testing

The flowability of the powders was expressed as the flow rate (mg/s) through a 3 mm orifice of the FlowPro device (iPAT, Turku, Finland). The flow rate was calculated by the FlowPro software based on the weight gain per unit of time registered by the analytical scale. Each sample was measured in threefold [15].

2.2.6.7. Helium pycnometry

The true density of the powders (ρ_t) was measured with an Accupyc II 1345 Helium pycnometer (Micromeritics, Norcross, USA) with an equilibration rate of 0.0050 psig/min and the number of purges set to 10.

2.2.6.8. Ratio model

To quantify the δ-mannitol content in the spray dried samples a ratio model was developed by linear regression of the ratio (I%) of the peak intensity of δ- and α-mannitol at 1054.9 cm^{-1} (I_δ) and 1027.9 cm^{-1} (I_α), respectively against the known δ/α concentration ratio. Peak intensity was corrected for the baseline intensity (I_{BL}):

$$I\% = I_\partial - I_{BL}/I_\propto - I_{BL}$$

The wave numbers were chosen to minimize interference from signals of the other compounds in the samples. The peak intensity at 985 cm^{-1} was selected as baseline-correction value (I_{BL}), since neither the mannitol polymorphs nor paracetamol showed an observable signal at this wave number [8,16]. 11 physical mixtures (2 g) with a known δ/α concentration and containing paracetamol were mixed in a Turbula T2F tumbling blender (W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 5 min at 30 rpm. Since the presence of paracetamol can influence the peak intensity of the Raman spectra, paracetamol was included in the model. The physical mixtures consisted of PCM-MAN (30:70 w/w), of which the mannitol part contained pre-defined δ/α ratios ranging from 0/1 to 1/0. A total of 11 physical mixtures was prepared. Raman spectra were recorded in triplicate. As stated by Campbell *et al*., it was assured that the particle size of the starting materials had a mean particle size < 125 µm, since larger particle sizes could disturb the peak intensity of the spectra [8].

2.2.6.9. Stability

Raman spectra of the samples were recorded after 2, 5, 8 and 11 months of storage at room temperature and ambient conditions and compared to the spectra recorded immediately after spray drying.

2.2.6.10. Characterization of the tablets

The hardness (expressed as the diametral crushing force of the tablet) (F), mass (m) thickness (t) and diameter (d) of the tablets (n = 10) were evaluated on a Sotax HT 10 combi tester (Sotax, Basel, Switzerland). Subsequently these parameters were used to calculate the tensile strength (TS) as stated by Fell and Newton [17]:

$$TS = 2F/\pi dt$$

The relative density of the tablets was calculated by dividing the apparent density of the tablet (ρ_a) *by* the true density of the powder (ρ_t). ρ_a was calculated as follows:

$$\rho_a = \frac{m}{\pi t D^2/4}$$

Due to the limited amounts of co-spray dried powders and tablets, no friability or disintegration testing was performed.

3. Results and discussion

3.1. Preliminary experiments

Most commercially available mannitol products consist of β-mannitol (e.g. Pearlitol 50 C), or a mixture of α- and β-mannitol for spray dried grades (e.g. Pearlitol 200 SD). As illustrated in Figure 1, the Raman spectrum of Pearlitol 50C is nearly indistinguishable from the spectrum of pure β-mannitol in literature. Similarly, the spectrum of Parteck Delta M practically overlaps with the spectrum of pure δ-mannitol. When comparing the Raman spectra of the pure polymorphs, β and α are most related. These polymorphs exhibited small differences in physicochemical properties and are both orthorhombic crystals. δ-mannitol has a monoclinic crystal structure, which is reflected in a more deviant Raman spectrum [4,8]. Spray drying of mannitol formulations always resulted in crystalline material.

Preliminary tests demonstrated that δ-mannitol could not be formed by spray drying pure mannitol solutions or suspensions at the applied process settings. After spray drying a pure mannitol solution (10% w/w) or suspension (40% w/w), the Raman spectra indicated mainly β-mannitol. δ-mannitol, identifiable by the characteristic peaks at 1054 cm^{-1} and 1145 cm^{-1} could not be detected (Figure 2).

The results are in line with the observations of Vanhoorne *et al*. and Hulse *et al*. where 5% w/w solutions of different commercially available mannitol grades were spray dried and none of them resulted in the presence of δ-mannitol [5,12,18].

3.2. Influence of the formulation on the formation of δ-mannitol

In the first set of experiments the influence of formulation composition on the formation of δ-mannitol was investigated using DOE. The main response was whether the δ-polymorph could be formed. Raman spectra identified δ-mannitol in each sample, marked by the characteristic peaks at 1054 cm^{-1} and 1145 cm^{-1} (Figure 3).

Except for the formulations with a low paracetamol content (N1, N2; PCM–MAN 1:99), the δ-polymorph was dominantly present (N3-N7). β-mannitol could only be detected for the formulations with a low paracetamol content (N1, N2; PCM–MAN 1:99), together with δ- and α-mannitol. This demonstrated that even a low paracetamol concentration was able to affect the crystallization process during spray drying, hence initiating the crystallization into δ-mannitol. It also revealed that δ-mannitol was also formed when a high paracetamol content (N3, N4; PCM-MAN 70:30) was present in the sample.

The effects of the total solids fraction appeared limited to the formulations containing PCM-MAN 1:99 and had no perceptible influence on δ-mannitol but affected the amount of β and α-mannitol. A 2% w/w solution (N1) resulted in a higher α-mannitol fraction compared to a 40% w/w suspension (N2). This can be attributed to the suspended fraction still containing the β-polymorph. It can be concluded that both the PCM-MAN ratio and the total solids fraction affected the final polymorph composition.

The fact that paracetamol can alter the crystallization behavior of mannitol could be attributed to its ability to react with water by hydrogen bonding. Therefore, it could prevent the water molecules from interacting with the OH-network of mannitol. Yoshinari *et al.* [7] investigated the mechanisms of polymorphic transition of δ-mannitol and the solvent dependency of this conversion. They suggested that water and other hydroxyl group-containing solvents can act as a molecular loosener on the δ-mannitol crystal lattice due to their ability to alter the hydrogen-bonding network, resulting in a conversion to the thermodynamically stable β-form. Similarly, adding an agent that can prevent water from reacting with the crystal network of mannitol could explain the formation of δ-mannitol during co-spray drying. This phenomenon was also observed by Vanhoorne *et al*. [13] during co-spray drying solutions of mannitol with PVP. Similarly, it was postulated by Hulse *et al.* [12] that obtaining δ-mannitol after co-spray drying mannitol with trypsin could be attributed to ion-dipole interactions of the protein with water. However, the exact mechanism of the solid-state conversion cannot yet be explained. Hulse *et al*. [12] also described that the physical state of mannitol after co-spray drying was independent of the trypsin protein content in a mannitol/trypsin range of ratio 1:9 to 9:1, but dependent on which protein was used, i.e., trypsin or lysozyme. Possibly this is due to differences in ion-dipole interactions between the different proteins, since lysozyme has more ionizable groups, thus

interacts more with water. Water and other solvents containing hydroxyl functions can alter the OH-network in the crystal lattice of mannitol, hence altering it to the dynamically favorable β-polymorph, as explained by Yoshinari *et al*. [7]. Dixon *et al*. [19] also noted effects of proteins on mannitol polymorphism during freeze drying. If the protein content increased from 1 to 5 mg/mL, the amount of δ-mannitol increased at the expense of β-mannitol.

3.3. Influence of process parameters on the formation of δ-mannitol

In the second set of experiments the influence of the airflow, nozzle atomization gas and inlet temperature on the formation of δ-mannitol was investigated for the PCM-MAN 30:70 formulation with a 20% w/w solids load and containing 0.1% w/w polysorbate 80. The δ-mannitol content after spray drying was quantified by a ratio model. Since β-mannitol could not be detected via Raman spectroscopy in any of the samples, the ratio model was solely built with δ- and α-mannitol. The absence of β-mannitol was confirmed on Raman spectra where the typical duo peak at 1118.8 and 1134.4 cm^{-1} is not perceptible (Fig. 4). A possible explanation could be that the formation of α-mannitol is linked to the initial dissolved mannitol concentration as described by Liao *et al*. [20,21]. They found the physical form of mannitol after freeze drying depended on the initial dissolved mannitol concentration: if low (< 1.5 – 3% w/w) the β form was dominant, if high (7.5% w/w) the α form was dominant. In this set of experiments the mannitol content is relatively high (14% w/w), which may contribute to the formation of α-mannitol after co-spray drying. The model was linearly fitted and had a correlation coefficient (R^2) of 0.98.

The process drying conditions of the 4M8-TriX and the Mobile Minor had similar effects on the formation of δ-mannitol. Figure 5 shows the effect plot on the formation of δ-mannitol for the screening DOE on the 4M8-Trix (N = 16, R^2 = 0.924, Q^2 = 0.882). The effects of airflow, inlet temperature and nozzle atomization gas can be interpreted as the change in response when varying a factor between its minimal and maximal setting, while keeping the rest of the factors constant. The uncertainty of the effect is indicated by a 95% confidence interval.

The drying capacity was inversely related to the formation of δ-mannitol. The airflow through the drying chamber appeared as the most influencing factor. When applying a higher airflow more α-mannitol and less δ-mannitol was formed. A shorter residence time in the drying chamber and harsher drying conditions were inversely correlated with the formation of δ-mannitol. Similar observations were reported in literature during freeze drying of mannitol solutions. Cannon and Trappler [10] found that slow cooling of a mannitol solution resulted in a δ/α mixture where δ-mannitol was dominant, whereas the opposite occurred at a high cooling rate. Poornachary *et al.* [22] studied the crystallization mechanism of mannitol in microdroplet evaporation and found that slow evaporation of aqueous

solution microdroplets could result in the formation of δ-mannitol [11,22,23]. Similarly, a longer residence time in the spray drying chamber and slower, less harsh drying of the droplet in combination with the ability of paracetamol to obstruct the water molecules from interacting with the mannitol crystal OH-network resulted in the formation of δ-mannitol during co-spraying. When droplets are dried at the harsh conditions, the shell formation of the droplet occurs earlier, resulting in a shorter constant-rate period where water can be directly evaporated form the droplet surface. As a result, the falling-rate period, where the remaining water in the droplet must be removed via diffusion through the shell, is prolonged. Therefore, the water molecules have more time to interact with the crystal formation of mannitol during drying.

The nozzle atomization gas, the second parameter in this part of the study, had a direct relationship with the δ-mannitol content in the samples. Increasing the nozzle atomization gas, thus creating smaller droplets, yielded a larger δ-mannitol fraction. The effect may be associated with the water content in the droplet that can interact with the crystal network during drying, and is linked to the droplet drying kinetics, as described previously. This effect is more pronounced for larger droplets that contain more water to interact with the forming lattice, resulting in a higher fraction of α-mannitol. At these harsher drying conditions it is also harder to dry larger droplets completely, which resulted in a lower process recovery (< 20%) [24,25].

Increasing the inlet temperature had a small inversely correlated effect on the formation of δ-mannitol. The effect was only pronounced at high airflow, but it was not considered significant since the uncertainty of the effect exceeded the 95% confidence interval.

In summary, formation of δ-mannitol was favored in the experiment with the lowest airflow, highest nozzle atomization gas and lowest inlet temperature. An overview of the experiments and their fraction of δ-mannitol calculated by the ratio model is given in Table 5. Due to the low recovery (< 10%) the experiments at airflow 0.6 m^3/min were limited to two in the design.

Scale-up to the pilot-scale spray dryer showed the same trends regarding the process parameters, but since airflow had the largest impact and this value could not be lowered any further, only a limited number of experiments were conducted. It must be noted that on the 4M8-TriX the maximal amount of δ-mannitol formed was 93%, whereas on the Mobile Minor this was only 59%. Since lowering the airflow on the Mobile Minor was not possible due to condensation in the drying chamber, this value was in this research not further optimized. However, the design of the spray dryer might also be of particular interest. While the tests were conducted with a formulation containing 30% paracetamol and 70% mannitol, maximizing the δ-mannitol formation for higher-dosed paracetamol formulations is likely possible.

Table 5. Overview process parameter experiments 4M8-TriX (DOE) and Mobile Minor. The selected formulations used for the tableting experiments are marked with an asterix (*).

Spray dryer	Experiment	Airflow (m^3/min)	Nozzle atomization gas (L/min)	Inlet temperature (°C)	δ (%)
4M8-TriX	P1	0.25	5.0	160	77
	P2*	0.25	7.5	160	82
	P3	0.25	12.5	160	93
	P4	0.43	5.0	160	19
	P5*	0.43	7.5	160	34
	P6	0.43	12.5	160	63
	P7	0.60	5.0	160	/
	P8	0.60	7.5	160	6
	P9	0.60	12.5	160	/
	P10	0.25	5.0	200	78
	P11	0.25	7.5	200	78
	P12	0.25	12.5	200	91
	P13	0.43	5.0	200	22
	P14	0.43	7.5	200	22
	P15	0.43	12.5	200	23
	P16	0.60	5.0	200	/
	P17	0.60	7.5	200	0
	P18	0.60	12.5	200	/
	P19	0.43	7.5	180	34
	P20	0.43	7.5	180	55
	P21	0.43	7.5	180	39
Mobile Minor	G1*	0.63	154	180	49
	G2	0.63	200	180	59
	G3	0.63	154	200	20
	G4*	0.71	154	180	4
	G5	0.84	154	180	0
	G6	1.03	154	180	0

3.4. Influence of binders on the formation of δ-mannitol

In the third set of experiments the influence of maltodextrin (MD) and hydroxypropyl methylcellulose (HPMC) on δ-mannitol formation was examined. However, neither MD nor HPMC inhibited the δ-mannitol formation in the evaluated concentrations. The characteristic δ-mannitol peak at 1054 cm^{-1} remains visible for all binder concentrations. No traces of other polymorphs are detectable. Hence, they can be used to generate directly compressible powders by co-spray drying (Figure 6).

3.5. Evaluation of the tablets

Four formulations (P2, P5, G1, G4) with acceptable content uniformity (90 – 110%) and recovery (> 60%) were selected for full powder characterization and tableting on the STYL'One compaction simulator together with two physical mixtures containing paracetamol and δ- and β-mannitol respectively (P-beta, P-delta) (Table 6). The flowability of the spray dried samples was poor due to slight agglomeration. Therefore, it was chosen to feed the compaction simulator manually.

Table 6 *Selected formulations for tableting experiments.*

Spray dryer	Code	δ (%)	True density (g/cm³)	d50 (µm)	Residual moisture (%)	Flowability (mg/s)	Content uniformity (%)
4M8-TriX	*P2*	82	1.4275 (± 0.0017)	45 (± 2)	0.98 (± 0.13)	11.6 (± 2.1)	98 (± 1)
	P5	34	1.4075 (± 0.0022)	47 (± 1)	1.33 (± 0.20)	9.8 (± 4.7)	97 (± 3)
Mobile Minor	*G1*	49	1.3928 (± 0.0027)	69 (± 2)	0.79 (± 0.21)	15.6 (± 4.4)	93 (± 1)
	G4	4	1.3897 (± 0.0018)	69 (± 2)	1.31 (± 0.11)	7.0 (± 0.2)	96 (± 1)

Compressibility, Tabletability and Compactability (CTC) profiles generated using the compaction simulator are shown in Figure 7. The compressibility plot denoted in Figure 7.a shows an increase in relative tablet density with increasing pressure. The extent of this increase was lower for P5, G4 and P-beta than for P2, G1 and P-delta. Due to the formation of δ-mannitol and the influence of co-processing, the co-spray dried powders exhibited better or similar tabletability profiles compared to the corresponding physical mixtures (Figure 7.b). The tablet tensile strength of the co-spray dried powders was superior to the physical mixture with β-mannitol, especially for P2 and G1 which contained the highest fractions of δ-mannitol. The tablets yielded maximal tensile strengths of 2.4 MPa for P2, 1.3 MPa for P5, 2.9 MPa for G1 and 1.1 MPa for G4, respectively, whereas the references resulted in maximal tensile strengths of 0.2 MPa for P-beta and 1.2 MPa for P-delta, respectively. Notable is that all co-spray dried powders exhibited a similar or better tabletability than P-delta, irrespective of their δ-mannitol content, which was attributed to the effect of co-processing. P2 and G1 on the one hand and P5 and G4 on the other hand result in similar tabletability, notwithstanding a substantial difference in δ-mannitol content. This could be due to the different drying conditions, i.e., laminar airflow on the 4M8-TriX vs. turbulent airflow on the Mobile Minor, or due to a different manner of encapsulation of paracetamol in the spray dryers. The compactability profile presented in Figure 7.c illustrated that P2 has a higher porosity than G1, resulting in a slightly weaker compact.

Monoclinic paracetamol, the thermodynamically stable commercially used form, is not suitable for direct compression. It is known to cause capping, which was observed for several tablets prepared with the physical mixtures. This was more pronounced for the physical mixtures with β-mannitol than for

those with δ-mannitol. SEM images indicated that it was possible to encapsulate the needle-shaped paracetamol crystals with mannitol during co-spray drying, making the effects of paracetamol less pronounced. Figure 8 comprises SEM images of both the starting material micronized paracetamol and the co-spray dried powders P2 and G1, produced on the 4M8-TriX and Mobile Minor, respectively. Where micronized paracetamol appeared as irregular and needle shaped in Figure 8 (a), this typical form was no longer prominently present after co-spray drying with mannitol (b, c).

3.6. Stability of delta-mannitol in co-spray dried powders

The spray dried powders were stored at ambient conditions (temperatures varying between 15 – 25°C) in sealed plastic bags for 11 months. No deviations were observed in the Raman spectra. The composition of the samples remained stable after 2, 5, 8 and 11 months. This is in accordance with the results of Burger *et al*. [4] reporting high kinetic stability of the metastable δ- and α-polymorphs; in their study no transformation into β-mannitol was observed during mechanical stress (compaction) or storage for more than five years at room temperature when kept dry. While polymorphic transitions are normally caused by heat or mechanical stress (e.g., friction, grinding, milling), mannitol polymorphs are resistant to most mechanochemical stresses due to the rigidly linked OH-network. Only a high uptake of a solvent containing hydroxyl groups is able to alter the OH-network [4,7,26].

4. Conclusion

This work has proven that it is possible to obtain δ-mannitol via co-spray drying with paracetamol, resulting in powders with improved tabletability compared to physical mixtures. It also indicated that the formation of δ-mannitol is strongly influenced by the process conditions, whereby airflow through the drying chamber was the most influencing factor. Formation of δ-mannitol was favored at low airflow, low inlet temperature and high nozzle atomization gas. The presence of even a small amount of paracetamol was sufficient to alter the crystallization behavior of mannitol during spray drying. Possibly this is due to the interactions by hydrogen bonding of paracetamol and water, preventing water to interact with the OH-bonds in the crystal network of mannitol.

Secondly, this work also highlighted the potential of co-spray drying prior to compression as all co-spray dried powders exhibited a similar or better tabletability than physical mixtures of paracetamol and δ-mannitol, irrespective of their δ-mannitol content, yielding tablets with a sufficiently high tensile strength.

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CRediT roles

Elisa De Pauw: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing-original draft, Writing – review and editing, Visualization. **Chris Vervaet:** Conceptualization, Methodology, Validation, Writing – Review and editing, Supervision, Project Administration. **Valérie Vanhoorne:** Conceptualization, Methodology, Validation, Writing – review and editing, Supervision, Project administration.

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Figure captions

Figure 1. Raman spectra of the starting- and reference materials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 2. Raman spectra of the spray dried solution (10% w/w), suspension (40% w/w) and reference materials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 3. Raman spectra of the DOE formulations and reference materials of the different polymorphs around (a) 1054 cm^{-1} and (b) 1145 cm^{-1}. Formulations with solids load 2% w/w are represented by a solid line, 40% w/w by a dotted line and 21% w/w by a dashed line. PCM-MAN 1:99 ratios are represented in yellow, 70:30 in grey and 35.5:64.5 in purple. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 4. Raman spectra of several experiments on both the 4M8-TriX and Mobile Minor spray dryer together with reference mannitol samples. The typical duo peak of β-mannitol at 1118.8 and 1134.4 cm^{-1} is not perceptible in the spray dried samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 5. The effect plot of the process parameter DOE (4M8-TriX) showing the effect of airflow, nozzle atomization gas and inlet temperature.

Figure 6. Raman spectra of the co-spray dried samples with MD (blue) and HPMC (pink) and a reference sample spray dried under the same process conditions (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 7. Compressibility (a), Tabletability (b) and Compactability (c) profiles of the co-spray dried materials and reference samples. Compacts were prepared of the co-spray dried powders P2 (4M8-TriX), P5 (4M8-TriX), G1 (Mobile Minor), G4 (Mobile Minor) and physical mixtures of PCM-β-MAN (P-beta) and PCM-δ-MAN (P-delta). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 8. Paracetamol micronized (a) has a typical needle shaped form, whereas for the co-spray dried powders on both the 4M8-TriX, P2 (b) and on the Mobile Minor, G1 (c) this shape is no longer visible, indicating encapsulation of suspended paracetamol crystals in the co-spray dried particles.