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European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 220–226
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Development of directly compressible powders via co-spray drying

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Received 14 September 2006; accepted in revised form 22 December 2006
Available online 18 January 2007

Abstract

Continuous production of directly compressible powders was achieved by coprocessing acetaminophen and carbohydrates via spray drying. Binary and ternary powder mixtures containing drug substance and carbohydrates were prepared by co-spray drying and evaluated on spray drying processibility, powder hygroscopicity, flowability, and compactability. The influence of process parameters during spray drying on the compaction behaviour of drug/excipient mixtures was investigated via Heckel analysis. Erythritol, lactose, maltodextrin, and mannitol were efficient in co-spray drying with acetaminophen. However, lactose mixtures showed poor flowability. Spray dried mixtures containing mannitol and erythritol were characterised as non-hygroscopic, highly dense, and good flowing powders. Mannitol increased tablet tensile strength in contrast with the poor compactability of erythritol. Maltodextrin was selected for further experiments because it provided excellent tablet tensile strength. The use of erythritol, maltodextrin and mannitol in binary drug/excipient mixtures resulted in high process yields. Compacts of erythritol, mannitol, and maltodextrin were characterised by higher tablet tensile strength at higher spray drying temperatures due to the increased particle fragmentation of erythritol and mannitol mixtures and to the increased plastic deformation of maltodextrin formulations. A combination of erythritol, maltodextrin, and mannitol was selected for further formulation and process optimisation of co-spray dried powders for direct compression.

Keywords: Coprocessing; Spray drying; Compression; Acetaminophen; Carbohydrates

1. Introduction

Tablets are still the most commonly used dosage form because of the ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids. Direct compression is the preferred method for the preparation of tablets because of several advantages. However, as specific material properties are required to allow direct compression, materials have been coprocessed via spray drying to obtain compounds having superior properties (hygroscopicity, flowability, and compactability) for direct compression compared to the individual excipients or their physical mixtures [1]. During coprocessing no chemical changes occur and all the reflected changes show up in the physical properties of the particles [2]. Several coprocessed excipients for direct compression are commercially available: ludipress (α-lactose monohydrate, polyvinylpyrrolidone, and crospovidone), Cellactose and Microcelac (α-lactose monohydrate and cellulose), Cel–O–Cal (cellulose and calcium sulphate), Prosolv (microcrystalline cellulose and silicon dioxide), and F-Melt (mannitol, xylitol, inorganic excipient, and disintegrating agent, developed for fast dissolving dosage forms) [3].

Hauschild and Picker [4] evaluated a coprocessed compound based on α-lactose monohydrate and maize starch for tablet formulation. Compared to its physical mixture the coprocessed material had a better flowability, a higher tablet tensile strength and a faster tablet disintegration. Heckel analysis showed that the spray dried mixture deformed plastically with limited elasticity, whereas the

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doi:10.1016/j.ejpb.2006.12.021

physical mixture exhibited a predominantly elastic behaviour.

Microcelac 100, a coprocessed spray dried filler/binder for direct compression and composed of 25% w/w microcrystalline cellulose and 75% w/w α-lactose monohydrate, showed superior flowability and binding properties compared to physical mixtures of microcrystalline cellulose with different lactose grades e.g. α-lactose monohydrate (lactose 100 M), anhydric β-lactose (Pharmatose DCL21), and spray dried lactose (Pharmatose DCL11) [5].

The purpose of this study was to improve the compactability of a poorly compressible drug substance by coprocessing with carbohydrates via spray drying. This report describes the influence of different excipients on the spray drying processibility and on the physico–chemical properties (hygroscopicity, flowability, and compactability) of binary and ternary mixtures containing drug substance and carbohydrates.

2. Materials and methods

2.1. Materials

Acetaminophen (Paracetamol dense powder) was received from Mallinckrodt Chemical Ltd. (Hazelwood, USA). Erythritol (C*Eridex 16955), isomalt (C*Isomaltidex 16500), mannitol (C*Mannidex 16700), and sorbitol (C*Sorbidex 16616) were donated by Cerestar (Mechelen, Belgium). Maltitol (Maltisorb®P90), maltodextrin (Glucidex®2), and xylitol (Xylisorb®90) were gifts from Roquette (Lestrem, France). Lactitol (Finlac™ DC) was supplied by Danisco (Copenhagen, Denmark). Lactose (Respitose® SV003) was obtained from DMV International (Veghel, The Netherlands). Magnesium stearate and colloidal silicon dioxide (Aerosil® 200) were purchased from Federa (Brussels, Belgium).

2.2. Methods

2.2.1. Preparation of the spray dried microparticles

Aqueous solutions of pure acetaminophen (total solid content: 1.2% w/w) and of acetaminophen and a carbohydrate (erythritol, isomalt, lactitol, lactose, maltitol, maltodextrin, mannitol, sorbitol, and xylitol) (drug/carbohydrate ratio: 1/1, total solid content: 2.4% w/w) were prepared. Spray drying of these solutions was performed in pilot plant mobile minor spray dryer (GEA NIRO, Copenhagen, Denmark). The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and 60° conical base. The solutions were fed to a two-fluid nozzle (diameter: 1 mm) at the top of the spray dryer by means of a peristaltic pump, type 520U (Watson Marlow, Cornwall, UK) and a Marprene® tubing (inside diameter: 4.8 mm) (Watson Marlow, Cornwall, UK). The spray dryer operated in co-current air flow. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature, sieved (375 μm) and stored in sealed vials (room temperature, ambient relative humidity) prior to their characterisation and further use. Pure acetaminophen and drug/excipient mixtures (1/1) containing erythritol, isomalt, lactitol, lactose, maltitol, maltodextrin, mannitol, sorbitol, and xylitol were prepared via spray drying using the parameters of process 1 (Table 1). To investigate the influence of spray drying parameters on the compaction behaviour of drug/excipient mixtures, binary solutions (1/1) containing erythritol, maltodextrin, and mannitol were co-spray dried via process 2 (Table 1). These settings were selected in order to decrease the residual moisture content of the spray dried powders using a higher drying air temperature and atomisation pressure.

In addition to the binary drug/carbohydrate powders, ternary powder mixtures were prepared via spray drying of aqueous drug/mannitol/excipient solutions and compared with drug/mannitol mixtures (1/1) produced according to process 2 (Table 1). Acetaminophen, mannitol, and a water soluble carbohydrate (erythritol and maltodextrin) were dissolved in demineralised water at room temperature (drug/mannitol/excipient ratio: 1/0.7/0.3 and 1/0.9/0.1, total solid content: 2.6% w/w). These solutions were spray dried according to process 2 (Table 1).

2.2.2. Evaluation of spray dried powders

X-ray diffraction (D-500, Siemens, Germany) with CuK_λ radiation (0.154 nm) was performed on the pure spray dried acetaminophen and the binary spray dried mixtures. The angular range (2θ) varied from 10 to 60° with steps of 0.02° and the measuring time was 1s/step.

The residual moisture content of the spray dried powders was determined via loss-on-drying using a Mettler LP16 moisture analyser, including an infrared dryer and a Mettler PM460 balance (Mettler-Toledo, Zaventem, Belgium). A powder sample of 5 g was dried at 105 °C during 15 min.

The hygroscopic behaviour of the powders was investigated by storing the spray dried powders in sealed boxes containing saturated salt solutions, which maintained a specific relative humidity depending of the salt. The salts used and the corresponding relative humidities are magnesium chloride (33.0% RH), magnesium nitrate (52.8% RH), ammonium nitrate (65.0% RH), sodium chloride (75.3% RH), and potassium chloride (84.3% RH). The moisture uptake was evaluated after 1 month via loss-on-drying (Mettler LP16 moisture analyser, including an infrared

Table 1
Process conditions during spray drying in the mobile minor spray dryer (GEA NIRO)

Process parameters	Process 1	Process 2
Feed rate (g/min)	30.5	38.5
Inlet drying air temperature (°C)	140	220
Outlet drying air temperature (°C)	60	80
Drying gas rate (kg/h)	80	80
Atomising air pressure (bar)	1	2
Compressed air flow (%)	55	50

dryer and a Mettler PM460 balance, Mettler-Toledo, Zaventem, Belgium). A sample of 1.5 g was dried at 105 °C during 30 min.

The thermal behaviour of the binary spray dried mixtures was compared with that of their physical mixtures using differential scanning calorimetry. Modulated temperature DSC experiments (heating rate: 2 °C/min, modulation amplitude: 0.5 °C, modulation period: 60 s and temperature range: −40 to 300 °C) were performed using a DSC 2920 calorimeter (TA Instrument, New Castle, USA) with a DSC refrigerated cooling system (TA Instruments, New Castle, USA).

The flowability of spray dried powders (*n*: 5) was measured according to the method described in the European Pharmacopoeia 5th ed. (automated powder flowability analyser, Type PTG-2, PharmaTest, Hainburg, Germany) using a 25 mm nozzle. An electrical stirrer (speed: 25 rpm) was used to avoid bridging in the funnel for material having poor flowability.

The bulk density of the spray dried powders was determined via the method described in the European Pharmacopoeia 5th ed. using 20 g of powder and a 100 ml graduated cylinder.

SEM images were recorded with a Quanta 200 FEG (FEI, Eindhoven, The Netherlands) scanning electron microscope operated at an acceleration voltage of 5 kV. The powder was deposited onto a carbon carrier substrate.

2.2.3. Tabletting process and evaluation

The spray dried powders were blended (TSA Turbula mixer, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 0.3% w/w colloidal silicon dioxide for 10 min in a first mixing step and with 0.5% w/w magnesium stearate for 5 min in a second mixing step. Glidant, lubricant, and spray dried powders were sieved (375 μm) before blending. The powder mixtures were compacted (*n*: 10, 500 ± 5 mg) on an excentric tablet press, Type EKO (Korsch, Berlin, Germany), equipped with 13.0 mm circular flat punches. The tablet properties were evaluated at two different compaction pressures (74 and 111 MPa).

Based on the diametral crushing strength of the tablets, determined using a hardness tester, Type PTB (Pharma Test, Hainburg, Germany), the tensile strength of the tablets was calculated according to Fell and Newton [6].

2.2.4. Heckel analysis

The porosity-compression pressure function according to Heckel was calculated. Flat-faced compacts (*n*: 3, 500 ± 5 mg, diameter: 13 mm) of drug/excipient mixtures produced according to processes 1 and 2 were prepared on a compaction simulator (ESH, Brierley Hill, UK) at maximum loads of 110 MPa. While the lower punch was stationary during compaction, the upper punch displacements followed a sine wave. The average punch speed during compaction was 3 mm/s. Data were compensated for punch deformation during compression. Final thickness and diameter of the tablets were measured with an electronic digital calliper (Bodson, Luik, Belgium). The true density was defined using a helium gas pykcometer, Accupyc 1330 (Micromeritics, Norcross). The following analysis parameters were used: 10 purges, 10 runs, and 19.5 psig as purge and run fill pressure. The Heckel equation (Eq. (1)) [7] is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the compactability of the powder bed as the product.

$$\mathrm{Ln}\ \frac{1}{1-D} = kP + A \tag{1}$$

where D is the relative density of a powder compact at pressure P. Slope k is a measure of the plasticity of a compacted material. Constant A is related to the die filling and particle rearrangement before deformation and bonding of the discrete particles. Thus, a Heckel plot allows for the interpretation of the mechanism of compression.

3. Results and discussion

Acetaminophen was used as model drug because of its poor compactability as evidenced during this study by the low tablet tensile strength (0.38 and 0.67 MPa at a compression pressure of 74 and 111 MPa, respectively) as well as capping and lamination problems after compaction of pure spray dried acetaminophen. This behaviour was due to the formation of monoclinic acetaminophen crystals during spray drying, exhibiting a relatively high elastic deformation [8]. Therefore, acetaminophen was coprocessed with water soluble carbohydrates to improve tablet tensile strength and to overcome capping and lamination problems.

The screened drug/excipient mixtures (1/1) were divided in three groups according to their spray drying processibility. Spray drying of drug/excipient mixtures (1/1) containing isomalt and sorbitol was not feasible because of process problems. Coprocessing of aqueous acetaminophen/sorbitol solutions (1/1) resulted in vitrification of sorbitol forming a transparent layer on the surface of the drying chamber wall, pipings, and cyclone. Powder mixtures containing isomalt completely blocked pipings and cyclone during spray drying as too much material accumulated in the pipings and cyclone. The second group consists of drug/excipient mixtures (1/1) composed of lactitol, maltitol and xylitol, which could be spray dried despite some process problems. Due to their gummy-like and thermoplastic nature, and high residual moisture content (Table 2), an important fraction of these binary powder mixtures adhered to the drying chamber wall surfaces, pipings, and/or cyclone, resulting in low process yields (lactitol: 40%, maltitol: 43%, xylitol: 61%) (Table 2). These problems occur regularly in spray drying operations [9] and can be caused by various factors: inappropriate drying resulting in high water content and sticky character of the spray dried powder, thermoplastic, and/or hygroscopic nature of the dried product under the temperature and humidity

Table 2
Spray drying process yield and residual moisture content after spray drying

Formulation	Yield (% w/w)	Residual moisture content (% w/w)
Acetaminophen/lactitol	40	2.90
Acetaminophen/maltitol	43	7.40
Acetaminophen/xylitol	61	4.72
Acetaminophen/erythritol	70	0.60
Acetaminophen/lactose	54	3.12
Acetaminophen/maltodextrin	82	7.10
Acetaminophen/mannitol	75	0.89

conditions within the drying chamber. The third group consists of erythritol, lactose, maltodextrin, and mannitol, which yielded non-sticky powders after co-spray drying with acetaminophen. In contrast to erythritol-, maltodextrin-, and mannitol-containing powders, lactose mixtures had a low yield probably caused by low drying temperatures. Normally lactose solutions or suspensions are spray dried at higher inlet and outlet drying temperatures of e.g. 170–190 °C and 85–100 °C, respectively [10–12]. Even for the best binary drug/excipient mixtures the process yield was below 90% (70, 82, and 75% for erythritol, maltodextrin and mannitol, respectively) (Table 2), which is economically unprofitable. However, it should be emphasised that spray drying was performed in a lab-scale drier which typically has a lower yield – in comparison to production scale spray dryers – due to higher wall deposits, since air residence times and radial distances from the atomiser to the drying chamber wall are shorter [9].

Because aqueous drug/excipient solutions (1/1) composed of isomalt, lactitol, maltitol, sorbitol, and xylitol were ineffective to coprocess via spray drying, only binary mixtures containing erythritol, lactose, maltodextrin, and mannitol were evaluated on powder hygroscopicity. Spray drying drug/excipient solutions (1/1) containing erythritol and mannitol resulted in crystalline non-hygroscopic powder mixtures (Fig. 1). Modulated DSC experiments showed fractions of amorphous lactose and completely amorphous maltodextrin in their corresponding spray dried drug/excipient mixtures. However, the drug/lactose mixtures were non-hygroscopic, while the use of maltodextrin resulted in a hygroscopic powder absorbing about 8.5% water at a relative humidity above 50% (Fig. 1).

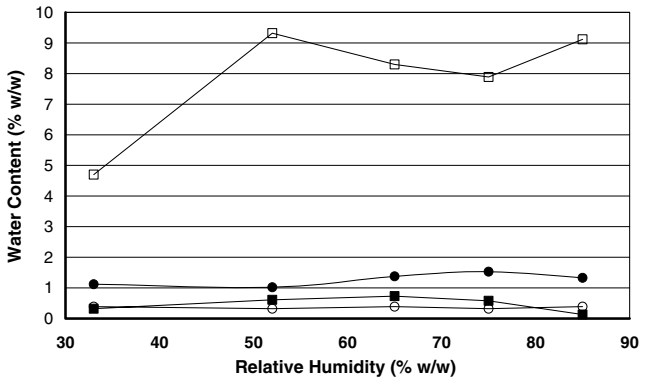

Fig. 1. Hygroscopicity of acetaminophen/excipient powder mixtures (1/1) containing erythritol (○), lactose (●), maltodextrin (□) and mannitol (■).

A good flowability of the powders is required to ensure a consistent tablet weight. Erythritol and mannitol binary mixtures were characterised by a powder flow time of 4.8 ± 0.7 and 5.9 ± 0.5 s/100 g, respectively, indicating acceptable flowability. Binary mixtures (1/1) containing maltodextrin illustrated poor flowability with a powder flow time of 76.6 ± 30.4 s/100 g. Powders containing lactose did not flow through the nozzle. Consequently, drug/lactose mixtures (1/1) were eliminated for further evaluation. The bulk densities of drug/excipient mixtures (1/1) containing erythritol, maltodextrin, and mannitol were 0.526, 0.192, and 0.439 g/ml, respectively. SEM pictures (Fig. 2) of drug/excipient mixtures containing erythritol and mannitol showed big oblong powder particles and irregular agglomerates, respectively, resulting in better powder flowability in comparison with the cohesive powder mixtures containing maltodextrin and lactose which consisted of small particles.

Coprocessing of acetaminophen with erythritol, maltodextrin or mannitol prevented tablet capping, and lamination, despite the fact that these binary mixtures contained monoclinic acetaminophen crystals, based on X-ray diffraction experiments. Powder X-ray data of pure monoclinic and orthorhombic acetaminophen have been proposed by Nichols and Frampton [13]. The orthorhombic acetaminophen polymorph, having better tabletting properties [14], was not formed during co-spray drying. The addition of maltodextrin and mannitol to the formulation improved tablet tensile strength in comparison with pure spray dried acetaminophen, whereas drug/erythritol mixtures provided comparable tablet tensile strength (Table 3). One-way ANOVA (SPSS 12.0) showed significant differences in tablet tensile strength between pure spray dried acetaminophen and drug/carbohydrate mixtures containing maltodextrin and mannitol as well as between binary mixtures composed of maltodextrin and mannitol.

Process conditions during spray drying (drying temperatures and atomisation pressure) affected the tabletting properties of acetaminophen/carbohydrate mixtures: at a compaction pressure of 74 MPa the tablet tensile strength was significantly higher when both the process temperature and the atomisation pressure were higher (Table 3). Compaction at 111 MPa showed a similar trend. The influence of these factors on the powder compactability was investigated using Heckel analysis (Table 4). As most pharmaceutical materials undergo particle fragmentation during initial loading followed by elastic and/or plastic deformation at higher loads [15], the fragmentation behaviour was evaluated by linear regression (R^2) of the initial phase of the compression (2–50 MPa). A decrease of R^2 indicates an increase of particle fragmentation, resulting in increased particle bonding surfaces. The reciprocal of the slope (P_y, yield pressure) of the linear part of the compression curve (40–110 MPa) reflected the total deformation [16], a

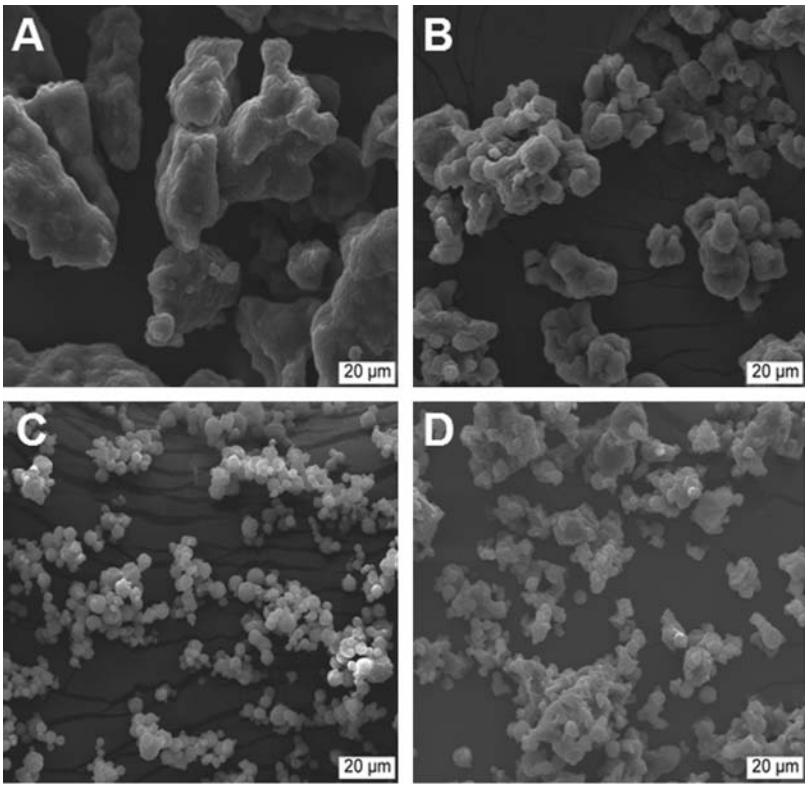

Fig. 2. SEM pictures of acetaminophen/excipient powder mixtures (1/1) containing erythritol (A), mannitol (B), maltodextrin (C) and lactose (D).

Table 3
Influence of spray drying parameters on tablet tensile strength (n: 10, means ± SD) Compression pressure: 74 MPa

Formulation	Tablet tensile strength (MPa)	
	Process 1	Process 2
Pure spray drying acetaminophen	0.38 ± 0.14	/
Acetaminophen/erythritol	0.45 ± 0.09	0.64 ± 0.16
Acetaminophen/maltodextrin	0.88 ± 0.15	2.39 ± 0.52
Acetaminophen/mannitol	0.72 ± 0.11	1.49 ± 0.21

decrease in yield pressure pointing to more plastic deformation behaviour [17]. Heckel analysis confirmed that the improved tablet tensile strength at higher process temperatures and atomisation pressure (process 2) was caused by an increased particle fragmentation of crystalline erythritol and mannitol mixtures, while an increased plastic deformation of amorphous maltodextrin formulations provided stronger tablets. Particles of an amorphous form were less prone to fragment but more deformable than crystalline particles [18,19].

Based on the characterisation of the spray dried binary powders and the influence of the different carbohydrates on the tablet properties, erythritol, maltodextrin, and mannitol were selected as excipients for the coprocessing of ternary mixtures with acetaminophen. In addition to the active ingredient, mannitol was used as the main fraction of these ternary mixtures, based on its positive effects on powder hygroscopicity, flowability, and compactability observed for the binary mixture. Erythritol or maltodextrin was added as third component to improve flowability and tablet strength, respectively, without a strong negative effect on process yield and/or powder hygroscopicity. The

Table 4
Heckel analysis (n: 3, means ± SD) of two component mixtures after co-spray drying using different process parameters

Formulation	Spray drying process	True density (g/ml)	Heckel analysis	
			R^2	P_y (yield pressure) (MPa)
Acetaminophen/erythritol	Process 1	1.3723	0.9663 ± 0.00156	129.1 ± 0.97
	Process 2	1.3762	0.9579 ± 0.00052	145.8 ± 2.91
Acetaminophen/maltodextrin	Process 1	1.4507	0.9720 ± 0.00063	135.7 ± 2.79
	Process 2	1.4776	0.9958 ± 0.00070	93.6 ± 1.65
Acetaminophen/mannitol	Process 1	1.3844	0.9785 ± 0.00058	129.9 ± 1.02
	Process 2	1.3864	0.9697 ± 0.00074	133.3 ± 0.53

lower content limit of erythritol and maltodextrin (drug/mannitol/excipient ratio: 1/0.9/0.1) was chosen to realise a significant improvement of flowability and tablet tensile strength, respectively, while the maximum content of erythritol and maltodextrin (drug/mannitol/excipient ratio: 1/0.7/0.3) was limited to avoid a strong negative influence on tablet tensile strength and hygroscopicity, respectively.

Spray drying of ternary mixtures containing erythritol and maltodextrin was extremely efficient and provided similar process yields (71–74%) in comparison with the reference formulation containing only drug and mannitol (ratio 1/1) (73%). The hygroscopic behaviour of the ternary mixtures was also similar to that of drug/mannitol mixtures (1/1): all were characterised as non-hygroscopic, only the maltodextrin formulations had a slightly higher but acceptable water uptake as a function of maltodextrin content (Fig. 3).

Powder flowability (Fig. 4) of all spray dried ternary mixtures was improved in comparison with the binary reference formulation. Using a higher concentration of erythritol or maltodextrin (ratio 1/0.7/0.3) showed better flowability in comparison with their corresponding formulations (ratio 1/0.9/0.1) because of increased particle size or sphericity, respectively. Similar to the binary mixtures the best flowability was obtained for formulations containing erythritol.

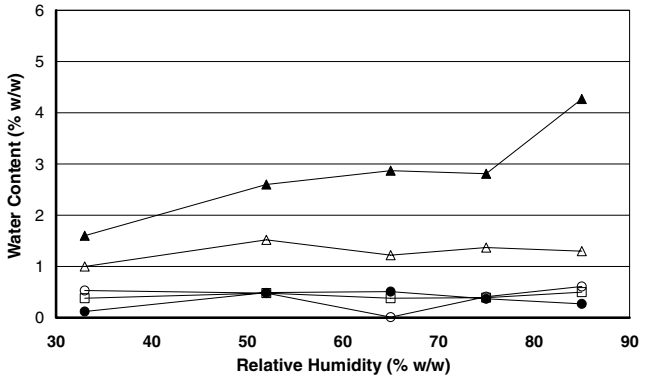

Fig. 3. Hygroscopicity of reference formulation (acetaminophen/mannitol powder mixture (1/1)) (□) and acetaminophen/mannitol/excipient powder mixtures containing erythritol (1/0.7/0.3) (●) and erythritol (1/0.9/0.1) (○), maltodextrin (1/0.7/0.3) (▲) and maltodextrin (1/0.9/0.1) (△).

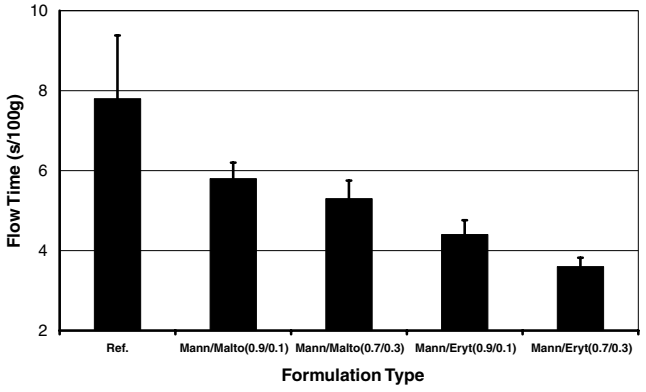

Fig. 4. Flowability of reference formulation (acetaminophen/mannitol powder mixture (1/1)) and acetaminophen/mannitol/excipient powder mixtures (1/0.7/0.3) and (1/0.9/0.1).

Table 5
Tablet tensile strength (n: 10, means ± SD) of reference formulation and ternary mixtures compression force: 74 MPa

Formulation	Tablet tensile strength (MPa)
Reference formulation: acetaminophen/mannitol (1/1)	1.49 ± 0.21
Acetaminophen/mannitol/maltodextrin (1/0.9/0.1)	1.50 ± 0.30
Acetaminophen/mannitol/maltodextrin (1/0.7/0.3)	2.19 ± 0.21
Acetaminophen/mannitol/erythritol (1/0.9/0.1)	0.99 ± 0.18
Acetaminophen/mannitol/erythritol (1/0.7/0.1)	1.12 ± 0.14

Tablet capping and lamination were not observed for compacts prepared from ternary powders. As expected from the evaluation of the binary mixtures, maltodextrin had a significantly positive effect on tablet tensile strength at the highest concentration, while erythritol had a significantly negative effect on compactability (Table 5).

Based on these results the compactability of powder mixtures containing acetaminophen and mannitol could be improved via the addition of maltodextrins, whereas a ternary mixture containing erythritol resulted in a strong improvement of flowability.

4. Conclusions

Coprocessing of acetaminophen/carbohydrate solutions via spray drying has demonstrated the efficiency of erythritol, maltodextrin, and mannitol to improve the physical properties and compactability of acetaminophen. Formulations containing mannitol had good flowability, a low hygroscopicity, and an acceptable tablet tensile strength. When formulating ternary drug/carbohydrate mixtures the powder flowability and tablet tensile strength could be improved by replacing part of the mannitol fraction by erythritol or maltodextrin, respectively.

Based on these observations a combination of mannitol, erythritol, and maltodextrin was selected for further formulation (ratio of different excipients) and process optimisation (process yield, flowability, and compactability) of these co-spray dried powders intended for direct compression.

Acknowledgments

The authors would like to thank K. Zuurman and Professor H.W. Frijlink, University of Groningen, Groningen, The Netherlands, for performing the compaction simulator tests.

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