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Research paper

Effect of maltodextrin and superdisintegrant in directly compressible powder mixtures prepared via co-spray drying

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Abstract

The effect of maltodextrins and superdisintegrants on the tablet properties was evaluated in directly compressible powders coprocessed via spray drying. Powder mixtures containing acetaminophen, mannitol, erythritol and different maltodextrin types were prepared via co-spray drying and physically mixed with crospovidone (6% w/w, Kollidon® CL) in order to evaluate the influence of maltodextrin grade (amylose/amylopectin ratio) on powder hygroscopicity, flowability, density and compactability. In addition, different superdisintegrant types and grades (6% w/w) were co-spray dried to evaluate their effect on tablet disintegration time. Tablet disintegration was affected by the amylose/amylopectin ratio of the maltodextrins. Tablets containing Glucidex® 2 (1–5% amylose) had a longer disintegration time compared to Glucidex® 9 (20% amylose) (11.8 min versus 5.7 min) and Unipure DC (50–70% amylose) (1 min). The disintegration time of tablets containing a coprocessed superdisintegrant was long due to loss of superdisintegrant during processing (preferential depositing on the spray dryer wall) and was in the following order: Kollidon® CL < Polyplasdone® XL < Explotab® < Kollidon® CL-M < Polyplasdone® XL-10 = Ac-Di-Sol®. A combination of acetaminophen, mannitol, erythritol, Glucidex® 9 and Kollidon® CL was selected for further formulation and process optimisation of co-spray dried powders intended for direct compression.

Keywords: Co-spray drying; Continuous processing; Maltodextrin; Superdisintegrant; Acetaminophen; Carbohydrates; Compression

1. Introduction

Coprocessing has been used to produce directly compressible powder mixtures with superior physico-chemical properties (flowability, hygroscopicity and compactability) compared to their physical mixtures or the individual excipients [1]. During coprocessing no chemical changes occur and the improved compression properties are due to the physical properties of the particles [2].

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 a good flowability, low hygroscopicity and 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 [3]. Based on these observations a combination of mannitol, erythritol and maltodextrin was selected for further formulation optimisation of these co-spray dried powders intended for direct compression. An increasing mannitol and erythritol content improved powder flowability and density. However, a higher erythritol concentration in the spray dried powder mixture had a negative influence on tablet tensile strength and friability. A higher maltodextrin content increased tablet tensile strength and improved tablet friability, while disintegration time, average particle size, powder flowability, density and hygroscopicity were negatively influenced [4].

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Maltodextrin, a partially hydrolysed starch, is composed of a mixture of amylose and amylopectin, both having a different influence on hygroscopicity and tablet properties such as tensile strength, friability and disintegration time [5–7]. Therefore, this report describes the influence of the maltodextrin grade (different amylose/amylopectin ratios) on powder hygroscopicity, flowability, density and compactability.

Since tablet disintegration is a prerequisite for a fast release of active ingredients from solid oral dosage forms, a disintegrant is routinely integrated into a formulation [8–10]. Based on this, the purpose of this study is also to improve the disintegration behaviour of tablets formulated using coprocessed powders via the incorporation of different superdisintegrants (type, particle size distribution) in the co-spray dried dispersion.

2. Materials and methods

2.1. Materials

Acetaminophen (Paracetamol dense powder) was received from Mallinckrodt Chemical Ltd. (Hazelwood, USA). Erythritol (C*Eridex 16955) and mannitol (C*Mannidex 16700) were donated by Cerestar (Mechelen, Belgium). Maltodextrin (Glucidex® 2, 9) was a gift from Roquette (Lestrem, France). Maltodextrin (Unipure DC HBA-28) was obtained from National Starch (Bridgewater, USA). Glucidex® 9 is a potato starch conversion product, containing 20% amylose and 80% amylopectin. Glucidex® 2 is a waxy maize starch conversion product, containing 1–5% amylose and 95–99% amylopectin, while Unipure DC is a high amylose maltodextrin (50–70% amylose and 30–50% amylopectin). Crospovidone was kindly donated by BASF (Kollidon® CL, CL-M, Ludwigshafen, Germany) or by ISP (Polyplasdone® XL, XL-10, Baar, Switzerland). Croscarmellose sodium (Ac-Di-Sol®) was donated by FMC (Brussels, Belgium) while sodium starch glycolate (Explotab®) was received from JRS Pharma (Rosenberg, Germany). 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 powders

Aqueous solutions of acetaminophen, mannitol, erythritol and maltodextrin (Glucidex® 2, 9, Unipure DC HBA-28) (total solid content: 2.6% w/w) were prepared to evaluate the effect of the maltodextrin grade. The contents of drug substance and carbohydrates in the formulations are listed in Table 1.

In addition to the evaluation of maltodextrins, where crospovidone was physically mixed with the spray dried powder mixture, aqueous suspensions (Table 2) of acetaminophen, mannitol, erythritol, maltodextrin (Glucidex® 9) and a superdisintegrant (croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate (Explotab®) and crospovidone (Kollidon® CL, CL-M, Polyplasdone® XL, XL-10)) (total solid content: 2.8% w/w) were coprocessed to evaluate the feasibility of co-spray drying with superdisintegrants and their effect on tablet disintegration time.

Table 1
Composition of the feed solution for the coprocessed formulations

	Maltodextrin grade selection (% of tablet composition)
Acetaminophen	46.5
Mannitol	11.6
Erythritol	20.9
Maltodextrin	14.0

The ratio between the different components is expressed as a percentage of the final tablet composition. Kollidon® CL (6% w/w) was physically mixed with the spray dried powders.

Table 2
Composition of the feed suspension for the coprocessed formulations

	Superdisintegrant type and grade selection (% of tablet composition)
Acetaminophen	46.5
Mannitol	24.6
Erythritol	13.9
Maltodextrin	7.9
Superdisintegrant	6.0

The ratio between the different components is expressed as a percentage of the final tablet composition.

Spray drying of these feeds 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/suspensions were fed to a two-fluid nozzle (diameter: 1 mm for maltodextrin experiments, 2 mm for superdisintegrant experiments) 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 aqueous feeds were prepared via a spray drying process, shown in Table 3. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature and stored (room temperature, ambient relative humidity) prior to their characterisation and further use.

Table 3
Process conditions during spray drying in the Mobile Minor spray dryer (GEA NIRO)

Process parameters	Setting
Feed rate (g/min)	46.6
Inlet drying air temperature (°C)	220
Outlet drying air temperature (°C)	70
Drying gas rate (kg/h)	80
Atomising air pressure (bar)	2
Compressed air flow (%)	50

2.2.2. Spray dried powder evaluation

The flowability ($n = 3$) (expressed as the flowability index ff_c in Eq. (1)) and bulk density ($n = 3$) of the powders were measured with a ring shear tester, Type RST-XS (Dietmar Schulze, Schüttgutmesstechnik, Wolfenbuttel, Germany). A detailed explanation of this technique can be found in Röck and Schwedes [11]. The powders were tested using three different consolidation stresses σ_1 (400, 1000, 1600 Pa) and a preshear of 2000 Pa. An ff_c-value below 1 indicates a non-flowing powder, between 1 and 2 a very cohesive powder, between 2 and 4 a cohesive powder, between 4 and 10 an easy flowing powder and higher than 10 a free flowing powder.

$$ff_c = \sigma_1/\sigma_c \quad (1)$$

where σ_1 is the consolidation stress and σ_c is the unconfined yield strength (compressive strength) of a bulk solid.

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 on the salt. The salts used and the corresponding relative humidities are magnesium chloride (33.0% RH), magnesium nitrate (52.8% RH), ammonia 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 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 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 average particle size (D_{50}) of each superdisintegrant type and grade was determined using dry powder (jet pressure: 2.8 bar, feed rate: 2 g) laser diffraction (Mastersizer, Malvern, Worchestershire, UK).

The superdisintegrant concentration ($n = 5$) in the co-spray dried powders was gravimetrically determined via a filtration procedure. A powder sample of 1.5 g was dispersed in 100 ml demineralised water. The fraction remaining in suspension (representing only the superdisintegrant since all other components dissolved in water) was isolated via filtration of the dispersion using glass fiber filters (GF 51, Scheicher & Schuell MicroScience, Dassel, Germany). The filters retained particles down to 1 μm and were over-dried (40 °C, 2 h) prior to use. After filtration these glass fiber filters were dried for 72 h at 40 °C and the amount of superdisintegrant retained by the filters was gravimetrically determined.

2.2.3. Tabletting process and evaluation

When evaluating the maltodextrin grade, the spray dried powders were blended (TSA Turbula mixer, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 0.5% w/w colloidal silicon dioxide and 6.0% w/w crospovidone (Kollidon® CL) for 10 min in a first mixing step and with 0.5% w/w magnesium stearate for 5 min in a second mixing step.

Formulations containing different superdisintegrant types and grades (theoretical disintegrant concentration in coprocessed powder: 6% w/w) were also co-spray dried to evaluate their effect on disintegration time. These co-spray dried powders were blended with 0.5% 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, disintegrant, lubricant and spray dried powders were sieved (375 μm) before blending. The powder mixtures were compacted on an excentric tablet press, Type EKO (Korsch, Berlin, Germany) equipped with 13.5 mm circular edged punches. The tablet properties were evaluated at a compression pressure of 74 MPa.

Based on the diametral crushing strength of the tablets (500 ± 5 mg), determined using a hardness tester, Type PTB (Pharma Test, Hainburg, Germany), the tensile strength of the tablets ($n = 10$) was calculated according to Fell and Newton [12]. Tablets ($n = 6$) were tested for disintegration time using a disintegrator, Type PTZ (Pharma Test, Hainburg, Germany). The test was performed in 900 ml demineralised water (37.0 °C ± 0.5 °C). Tablet friability was tested on 10 tablets ($n = 3$) using a friabilator, Type PTF (Pharma Test, Hainburg, Germany).

3. Results and discussion

3.1. Maltodextrin grade selection

Gonnissen et al. [4] applied mixture design to develop regression models for powder flowability, density, hygroscopicity, tablet tensile strength, disintegration time and friability of powder mixtures containing acetaminophen, mannitol, erythritol and maltodextrin (Glucidex® 2) produced via co-spray drying. Numerical optimisation was performed using statistical models to find the optimal formulation. According to the statistical prediction this optimal formulation (Table 1) was selected to evaluate the effect of maltodextrins on the hygroscopicity, flowability, density and compactability in directly compressible powders coprocessed via spray drying.

Spray drying 4-component solutions containing Glucidex® 2 or 9 resulted in a similar water uptake of all formulations, absorbing about 3.5% water (Fig. 1). As the water sorption in drug/carbohydrate mixtures (ratio 1:1) containing mannitol and erythritol was limited [3], the hygroscopicity of these 4-component mixtures at a relative humidity of 85% is mainly due to the maltodextrin fraction in the spray dried powder. In the spray dried powder containing high amylose maltodextrin (Unipure DC), water uptake was significantly lower compared to formulations containing Glucidex® 2 and 9. Mani and Bhattacharya [7] evaluated that the water absorption of injection moulded starch/synthetic polymer blends decreased as the amylose

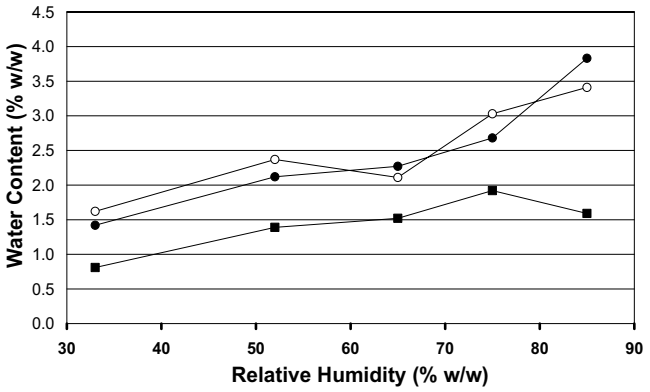

Fig. 1. Hygroscopicity of acetaminophen/mannitol/erythritol/maltodextrin powder mixtures (1/0.25/0.45/0.30) containing Glucidex® 2 (○), Glucidex® 9 (●) and Unipure DC HBA-28 (■).

content increased in the starch blends. Similarly, Ke et al. [13] stated that blends of polylactic acid and high amylose starch had a lower water absorption than blends of normal and waxy corn starches (high amylopectin starches).

The flowability index (ff_c) and density of the spray dried mixtures composed of Glucidex® 2 (6.8 ± 0.1, 0.442 ± 0.005 g/ml, respectively) and Glucidex® 9 (7.2 ± 0.1, 0.472 ± 0.007 g/ml, respectively) were similar, while formulations containing Unipure DC showed a significantly higher powder density (0.524 ± 0.007 g/ml) whereas powder flowability (ff_c: 6.4 ± 0.2) is decreased.

Coprocessing of acetaminophen with erythritol, maltodextrin and mannitol prevented tablet capping and lamination, despite the fact that these co-spray dried mixtures contained monoclinic acetaminophen crystals. Tablet properties were mainly determined by the maltodextrin content [4]. Tablet tensile strength and friability (Table 4) of formulations containing Glucidex® 2 and 9 were similar. However, Unipure DC lowered tablet tensile strength, whereas friability was increased. One-way ANOVA (SPSS 12.0) showed significant differences in tablet tensile strength between all three formulations. In addition, disintegration time was significantly affected by the amylose/amylopectin ratio (Table 4). Tablets containing Glucidex® 2 (1–5% amylose) had a longer disintegration time compared to Glucidex® 9 (20% amylose) (11.8 min versus 5.7 min) and Unipure DC (50–70% amylose) (1 min). Mollan and Çelik [14,15] stated that the slow disintegration of maltodextrin-containing (25.0–99.5% w/w) tablets was not controlled by the porosity of the tablet, but by a gel layer which formed around the tablet on immersion into water. This layer limited water penetration and was the controlling factor in disintegration behaviour of maltodextrin-containing tablets. Herman et al. [5,6] evaluated the influence of amylose/amylopectin ratio on the drug release of starch-containing tablet formulations. A minimal amount of amylose seemed to be an essential component to achieve high gel hardness while amylopectin seemed to be responsible for the cohesive character of the gel [5].

Table 4
Influence of maltodextrin grade on tablet tensile strength ($n = 10$, mean ± SD), tablet friability ($n = 3$, mean ± SD) and tablet disintegration time ($n = 6$, mean ± SD)

Formulation	Tensile strength (MPa)	Friability (%)	Disintegration time (min)
Glucidex® 2	1.92 ± 0.13	0.46 ± 0.12	11.8 ± 3.2
Glucidex® 9	2.15 ± 0.16	0.56 ± 0.12	5.7 ± 0.1
Unipure DC	1.41 ± 0.12	1.07 ± 0.26	1.0 ± 0.1

Compression pressure: 74 MPa.

Based on the characterisation of the powder mixtures containing different maltodextrin grades, Glucidex® 9 was selected as maltodextrin for coprocessing in combination with acetaminophen, mannitol and erythritol. Glucidex® 9 provided an excellent tablet disintegration time in combination with a high tablet tensile strength, low friability and acceptable powder hygroscopicity, flowability and density of the spray dried powders.

3.2. Superdisintegrant type and grade selection

Because tablet disintegration was mainly determined by the maltodextrin content and type, the maltodextrin content in the selected formulation was decreased in order to optimise disintegration time. Therefore, numerical optimisation was applied to adjust the levels of mannitol, erythritol and maltodextrin resulting in the formulation shown in Table 2 [4]. Aqueous suspensions of acetaminophen, mannitol, erythritol, maltodextrin (Glucidex® 9) and a superdisintegrant (croscarmellose sodium, sodium starch glycolate, crospovidone) were prepared. Whereas the drug and polyols dissolved in the aqueous medium, the dispersed superdisintegrants swelled in the aqueous feed, Zhao and Augsburger [8] reported that the aqueous swelling capacity of superdisintegrant was in the following order: sodium starch glycolate (increase in diameter: 251%) > croscarmellose sodium (104%) ≫ crospovidone (29%). These coarser droplets dry insufficiently during processing to acquire dry surfaces and therefore deposited on the wall of the spray dryer. Loss of the three superdisintegrant ranged from 20 to 77% w/w in relation to its initial content in the feed. The higher the average particle size of swollen superdisintegrant in the aqueous feed, the lower is the content of superdisintegrant in the spray dried powder, resulting in lower process yields (Table 5). 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 [16]. Thus, the small test spray dryers (Mobile Minor) limit the particle size that can be successfully dried. Coarser powder from the same atomiser device can always be handled in the larger industrial dryer, and thus the inability to produce a desired particle specification in a pilot plant test does not automatically rule out a successful operation on a larger scale. In addition, co-spray drying of acetaminophen,

Table 5
Average particle size, D_{50}, (average particle size after swelling in an aqueous medium according to the swelling coefficients of Zhao and Augsburger [8]) of disintegrant, disintegrant content in spray dried powder in relation to its initial content in the feed ($n = 5$, mean ± SD), yield, residual moisture content and tablet disintegration time ($n = 6$, mean ± SD)

	Disintegrant		Spray dried powder		Tablet disintegration time (min)
	Average particle size (μm)	Concentration in spray dried powder (% w/w)	Yield (% w/w)	Residual moisture content (% w/w)	
Ac-Di-Sol®	49.0 (96.1)	76.7 ± 5.0	78.1	2.5	[a]
Explotab®	46.4 (162.9)	20.0 ± 1.7	62.1	3.4	18.0 ± 1.7
Kollidon® CL	99.1 (127.8)	41.7 ± 6.7	68.1	2.1	14.5 ± 0.5
Kollidon® CL-M	6.1 (7.9)	135.0 ± 5.0	76.3	2.1	18.3 ± 0.7
Polyplasdone® XL	107.4 (138.5)	26.7 ± 8.3	66.5	1.6	17.0 ± 0.7
Polyplasdone® XL-10	21.1 (27.2)	68.3 ± 8.3	67.9	2.8	[a]

Compression pressure: 74 MPa.
[a] Tablets were not completely disintegrated within 20 min.

mannitol, erythritol, maltodextrin and a superdisintegrant in a production-scale spray dryer will be presented in future work.

Despite a decrease in maltodextrin concentration, the disintegration time of tablets containing co-spray dried superdisintegrant was high due to loss of disintegrant during processing (Table 5) in combination with the specific disintegration mechanisms. Tablet disintegration is based on mechanisms including water wicking, swelling, deformation recovery, repulsion and heat of wetting and depending on average particle size, porosity, swelling capacity, rate and extent of water uptake [8]. However, no single mechanism is applicable to all disintegrating agents. It is likely that in most cases, a combination of mechanisms is taking place simultaneously [9]. Despite their high hydration capacities [8] Ac-Di-Sol® and Explotab® were less effective for tablet disintegration, probably their swelling formed to a gel which blocked tablet pores and prevented further penetration of water into the inner layers of the tablet. Tablets containing crospovidone (Kollidon® CL) disintegrated faster (Table 5). Kornblum and Stoopak [17] observed that crospovidone swelled very little in comparison with Ac-Di-Sol® and Explotab®, yet absorbed water rapidly into its pore network. Crospovidone particles with their porous particle morphology quickly wick water into their capillaries to generate the rapid volume expansion and hydrostatic pressures that caused tablet disintegration.

Due to its faster disintegration crospovidone was selected for further evaluation and crospovidone grades having different average particle size were compared. The disintegration time of tablets containing different coprocessed crospovidone grades was in the following order: Kollidon® CL < Polyplasdone® XL < Kollidon® CL-M < Polyplasdone® XL-10 (Table 5). Although the loss of crospovidone during co-spray drying depended on their average particle size in the feed suspension, formulations containing different crospovidone grades showed no correlation between the residual disintegrant content in the spray dried powder and tablet disintegration time, because the disintegration potential is also depending on average particle size, porosity, swelling capacity, rate and extent of water uptake [8].

It has been reported in the literature that larger sized disintegrant particles are more efficient than smaller particles of the same material due to a difference in swelling pressure [18]. Although the coarse crospovidone grades (Kollidon® CL and Polyplasdone® XL) had a similar average particle size (99 versus 107 μm, respectively), formulations containing Kollidon® CL resulted in a faster tablet disintegration because of their higher content in the spray dried powder in comparison with Polyplasdone® XL.

In comparison with Kollidon® CL and Polyplasdone® XL, tablets containing Polyplasdone® XL-10 had a longer disintegration time related to the reduction in average particle size and thus disintegration potential [18], despite their higher content in the spray dried powder. Kollidon® CL-M and Polyplasdone® XL tablets had comparable disintegration times, despite the limited disintegration potential of the smaller Kollidon® CL-M particles. This was compensated by its feasibility for co-spray drying in a lab-scale spray dryer resulting in a high content of Kollidon®CL-M in the spray dried powder.

4. Conclusions

A combination of erythritol, mannitol, maltodextrin (Glucidex® 9) and a superdisintegrant (Kollidon® CL) was selected for further formulation and process optimisation (process yield, flowability and compactability) of co-spray dried powders for direct compression. Glucidex® 9 was selected as maltodextrin type because it improved tablet disintegration in combination with acceptable physicochemical powder properties, tablet hardness and friability, while Kollidon® CL minimised tablet disintegration time.

In addition, co-spray drying of acetaminophen, mannitol, erythritol, maltodextrin and a superdisintegrant in a lab-scale spray dryer yielded powders with a significant and representative loss of superdisintegrant depending on its average particle size after swelling in an aqueous medium. However, when coprocessing a superdisintegrant

(Kollidon® CL-M) with an average particle size in swollen state adjusted to the spray dryer dimensions and residence time, all dispersed superdisintegrant was collected. During scaling-up in a production scale spray dryer, the average particle size of superdisintegrant feasible to co-spray dry without loss (deposits) will increase significantly resulting in lower disintegration times.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2007.05.004.

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