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Mixture Design Applied to Optimize a Directly Compressible Powder Produced via Cospray Drying

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Coprocessing via spray drying was applied to improve the compactability of acetaminophen and to select an optimal formulation. Four-component mixtures containing acetaminophen, mannitol, erythritol, and maltodextrin were produced by cospray drying. A D-optimal mixture design was constructed to evaluate the spray dried powder and tablet properties. 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.

Keywords cospray drying; mixture design; acetaminophen; carbohydrates; compression

INTRODUCTION

Coprocessing has been used to produce directly compressible powder mixtures with superior physicochemical properties (flowability, hygroscopicity, and compactability) compared with their physical mixtures or the individual excipients (Gohel & Jogani, 2003). During coprocessing no chemical changes occur and the improved compaction properties are due to the physical properties of the particles (Gohel, 2005).

Several coprocessed excipients for direct compression are commercially available: Avicel CE 15 (microcrystalline cellulose and guar gum), Starlac (α-lactose monohydrate and maize starch), Di-pac (sucrose and dextrin), Pharmatose DCL 40 (anhydrous lactose and lactitol), and F-Melt (mannitol and xylitol; an inorganic excipient and disintegrating agent developed for fast-dissolving dosage forms; Tanaka, Nagai, Kawaguchi, Fukami, & Hosokawa, 2005).

Gohel and Jogani (2003) developed a multifunctional, coprocessed, directly compressible excipient containing lactose, polyvinylpyrrolidone, and croscarmellose sodium. This product had a better flowability, compactability, and tablet disintegration than lactose monohydrate. Hauschild and Picker (2004) found that a coprocessed mixture of α-lactose monohydrate and maize starch showed a better flowability, higher tablet tensile strength, and faster tablet disintegration. Heckel analysis showed that the spray dried mixture deformed plastically with limited elasticity, whereas the physical mixture exhibited a predominantly elastic behavior.

Cellactose, a coprocessed spray dried filler/binder for direct compression, composed of 25% w/w powdered cellulose and 75% w/w α-lactose monohydrate, had a higher tablet tensile strength compared with physical powder mixtures containing 25% w/w Elcema P-100 and 75% w/w lactose for direct compression (Tablettose; Belda & Mielck, 1996).

In addition to the coprocessing of excipients in order to improve their physicochemical properties, Gonnissen and colleagues (2007) developed cospray dried drug substance/excipient(s) mixtures. Coprocessing of acetaminophen/carbohydrate solutions has demonstrated the efficiency of mannitol, erythritol, and maltodextrin to improve the physical properties and compactability of acetaminophen. Formulations containing mannitol had a good flowability, a low hygroscopicity, and an acceptable tablet tensile strength. When formulating ternary drug/carbohydrate mixtures, the powder flowability and tablet strength could be improved by replacing part of the mannitol fraction by erythritol or maltodextrin, respectively (Gonnissen, Remon, & Vervaet, 2007).

Based on these observations, a combination of mannitol, erythritol, and maltodextrin was selected for further formulation optimization (residual moisture content, process yield, powder flowability, average particle size, density, hygroscopicity, and compactability) of these cospray dried powders intended for direct compression.

The goal of this study is to optimize the ratio of the different excipients in a formulation containing acetaminophen in order to improve the physicochemical properties of the spray dried powder and its corresponding tablet properties. Mixture design was used as the statistical tool for finding the optimal composition (Huisman et al., 1984).

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MATERIALS AND METHODS

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), and maltodextrin (Glucidex® 2, DE: maximum 5) was a gift from Roquette (Lestrem, France). This maltodextrin grade consisted of 1% to 5% amylose and 95% to 99% amylopectin. Crospovidone (Kollidon® CL) was kindly donated by BASF (Ludwigshafen, Germany), and magnesium stearate and colloidal silicon dioxide (Aerosil® 200) were purchased from Federa (Brussels, Belgium).

Methods

Preparation of the Spray Dried Microparticles

Aqueous four-component solutions (total solid content: 2.6% w/w) containing a fixed concentration of acetaminophen (46.5% w/w of tablet composition) and variable concentrations of mannitol, erythritol, and maltodextrin were prepared by dissolving all components in demineralized water at room temperature. The contents of the carbohydrates in the formulations are listed in Table 1. Spray drying of these solutions was performed in a 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 a 60° conical base. The solutions were fed to a two-fluid nozzle (1-mm diameter) at the top of the spray dryer by means of a peristaltic pump, type 520U (Watson Marlow, Cornwall, UK) and a Marprene® tubing (4.8-mm inside diameter; Watson Marlow, Cornwall, UK). The spray dryer operated in concurrent airflow. 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 characterization and further use. The solutions were spray dried according to the process conditions shown in Table 2.

Experimental Design

Data from a previous study were used to construct the mixture design (Gonnissen et al., 2007). In addition to the active ingredient, mannitol was used because of its positive effects on powder hygroscopicity, flowability, and compactability observed for the binary and ternary mixtures. Erythritol and maltodextrin were added to improve flowability and tablet tensile strength, respectively. The mannitol content varied between 0% and 32.55% w/w, while the erythritol and maltodextrin fraction changed from 9.30% to 41.85% w/w and from 4.65% to 23.25% w/w, respectively. The lower content limit of erythritol was chosen to realize a significant improvement of flowability and density, while a minimum maltodextrin content of 4.65% w/w was used to increase tablet tensile strength. The maximum content of erythritol was limited to avoid a strong negative influence on tablet tensile strength and the maximum content of maltodextrin was limited to avoid a strong negative influence on hygroscopicity.

Because the experimental space is irregular, classical mixture designs such as the simplex lattice and the simplex centroid could not be applied. Therefore, a D-optimal mixture

TABLE 1
Compositions of the Mixture Design Experiments

	Components		
Run	A: X_1: Mannitol (% of Tablet Composition)	B: X_2: Erythritol (% of Tablet Composition)	C: X_3: Maltodextrin (% of Tablet Composition)
1	23.25	9.30	13.95
2	16.28	25.58	4.65
3	0	41.85	4.65
4	0	23.25	23.25
5	11.63	20.93	13.95
6	0	32.55	13.95
7	32.55	9.30	4.65
8	17.44	15.11	13.95
9	5.81	26.74	13.95
10	6.98	16.27	23.25
11	32.55	9.30	4.65
12	16.28	25.58	4.65
13	0	41.85	4.65
14	0	23.25	23.25
15	13.95	9.30	23.25

In addition to the carbohydrates, each formulation contained 46.5% (w/w of tablet composition) acetaminophen. After spray drying, the powders were blended with colloidal silicon dioxide (0.5%), crospovidone (6%), and magnesium stearate (0.5%).

TABLE 2
Process Conditions During Spray Drying in the Mobile Minor Spray Dryer (GEA NIRO)

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

design was selected (Lewis & Chariot, 1991; Bodea & Leucata, 1997). Because interactions between the variables were expected, the following special cubic model in Equation 1 was proposed:

$$Y = \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{2} \sum_{j=i+1}^{3} \beta_{ij} X_i X_j + \beta_{123} X_1 X_2 X_3 \qquad (1)$$

where Y is the response, X_i and X_j are the relative fractions of components *i* and *j*, respectively, in the mixture, and β_i, β_{ij}, and β_{123} are the coefficients.

The candidate points were chosen by the software (Design-Expert version 6.0.10, Stat-Ease, Minneapolis, USA) and were: vertices (4), centers of the edges (4), thirds of the edges (8), axial check blends (4), interior blends (4), and overall centroid (1). From the 25 candidate points, 7 runs were chosen to establish the model, 4 runs for measuring the lack-of-fit, and 4 runs were replicated for the experimental error, generating a total of 15 runs. This enabled the evaluation of the appropriate regression model. Manual regression was performed. The highest order significant polynomial (significance threshold: .05) was selected, where only significant model terms were included without destroying the model hierarchy. The outlier-t limit was set at 3.5. The significant model was used for fitting the response. The lack-of-fit test and a normal probability plot of the residuals were performed in order to evaluate the model and to detect outliers. The models provide several comparative measures for model selection. R^2 statistics, which give a correlation between the experimental response and the predicted response, should be high for a particular model to be significant. Adjusted R^2, which gives similar correlation after ignoring the insignificant model terms, should have good agreement with predicted R^2 for the model to be fit (Hicks & Turner, 1999). Predicted and adjusted R^2 should be within 0.20 of each other (Manual Design-Expert version 6.0.10.). Contour plots for the response were drawn for determining the optimal content levels of the components.

The different responses were residual moisture content, process yield, powder flowability, average particle size, density, hygroscopicity, tablet tensile strength, disintegration time, and friability.

Spray Dried Powder Evaluation

The flowability ($n = 3$; expressed as the flowability index ff_c in Equation 2) 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 (2005). The powders were tested using three different consolidation stresses σ_1 (400, 1,000, and 1,600 Pa) and a preshear of 2,000 Pa. An ff_c-value below 1 indicates a nonflowing 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.

$$ff_c = \sigma_1 / \sigma_c \qquad (2)$$

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

The average particle size (D_{50}) and span of each spray dried powder was determined using dry powder (jet pressure = 2.8 bar, feed rate = 2 g) laser diffraction (Mastersizer, Malvern, Worchestershire, UK).

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

The hygroscopic behavior of the powders was investigated by storing the spray dried powders in sealed boxes containing saturated salt solutions, which maintained a specific relative humidity dependent on the salt. The salts used and the corresponding relative humidities were 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 one month via loss-on-drying (Mettler LP16 moisture analyzer, including an infrared dryer and a Mettler PM460 balance, Mettler-Toledo, Zaventem, Belgium). A sample of 1.5 g was dried at 105 °C for 30 minutes.

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.

Tabletting Process and Evaluation

The spray dried powders were first blended (TSA Turbula mixer, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 0.5% w/w colloidal silicon dioxide and 6.0% w/w crospovidone for 10 minutes and then with 0.5% w/w magnesium stearate for 5 minutes. Glidant, disintegrant, lubricant, and spray dried powder were sieved (375 μm) before blending. The powder mixtures were compacted on an excentric tablet press (Type EKO, Korsch, Berlin, Germany) equipped with 13.0-mm circular flat 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 (1968). Tablets ($n = 6$) were tested for disintegration time using a disintegrator (Type PTZ, Pharma Test, Hainburg, Germany). The test was performed in 900 ml demineralized 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).

RESULTS AND DISCUSSION

Summary Statistics for the Model

Analysis of variance of the responses (Table 3) indicates that response surface models developed for powder flowability, average particle size, density, hygroscopicity, tablet tensile strength, disintegration time, and friability were significant and adequate, without significant lack of fit. Transformation of average particle size (power transformation, λ: 2.31) and tablet disintegration time (logarithmic transformation) responses were needed because the residuals were a function of the magnitude of the predicted values.

Table 4 details the model summary statistics for the selected significant models. It can be observed that, with exception of tablet friability, R^2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2 value is in good agreement with the adjusted R^2 value, resulting in reliable models.

Since the ability to spray dry a product to a specific residual moisture content at a given outlet drying air temperature depends upon the humidity of the air leaving the drying chamber (which is the sum of the moisture in the atmospheric air entering the dryer and the amount of moisture created during the spray evaporation; Masters, 2002), daily changes of ambient humidity conditions could affect the residual moisture content in the spray dried powder (Table 5). As a result, the model estimating residual moisture content was not significant.

TABLE 3
ANOVA—Influence of Formulation Composition on the Response Factors

Response Factor	Model F-value	$p > F$	Lack of Fit F-value	$p > F$
Flowability	18.31	0.0002	3.31	0.1347
Average particle size (D_{50} ; μm)	36.80	< 0.0001	1.68	0.3220
Density (g/ml)	57.71	< 0.0001	4.29	0.0889
Hygroscopicity (33% RH; %)	30.54	< 0.0001	1.56	0.3511
Hygroscopicity (52% RH; %)	231.78	< 0.0001	0.41	0.8682
Hygroscopicity (65% RH; %)	207.46	< 0.0001	1.69	0.3214
Hygroscopicity (75% RH; %)	446.55	< 0.0001	0.99	0.5415
Hygroscopicity (85% RH; %)	178.98	< 0.0001	2.59	0.1873
Tablet tensile strength (MPa)	53.82	< 0.0001	2.35	0.2130
Tablet disintegration time (s)	101.93	< 0.0001	1.30	0.4126
Tablet friability (%)	10.69	0.0026	1.23	0.4784

TABLE 4
Model Summary Statistics—Influence of Formulation Composition on the Response Factors

Response Factor	SD	R^2	Adjusted R^2	Predicted R^2
Flowability	0.51	0.9105	0.8608	0.7826
Average particle size (D_{50}; μm)	892.13	0.8700	0.8464	0.7867
Density (g/ml)	0.029	0.9130	0.8972	0.8413
Hygroscopicity (33% RH; %)	0.29	0.8358	0.8084	0.7476
Hygroscopicity (52% RH; %)	0.19	0.9748	0.9706	0.9554
Hygroscopicity (65% RH; %)	0.21	0.9719	0.9672	0.9591
Hygroscopicity (75% RH; %)	0.19	0.9867	0.9845	0.9769
Hygroscopicity (85% RH; %)	0.36	0.9676	0.9622	0.9495
Tablet tensile strength (MPa)	0.25	0.8997	0.8830	0.8572
Tablet disintegration time (s)	0.087	0.9826	0.9730	0.9462
Tablet friability (%)	0.22	0.6602	0.5984	0.4944

TABLE 5
Response Results, Average Particle Size, and Bulk Density for Mixture Design Experiments

	Responses				
Run	Residual Moisture Content (% w/w)	Process Yield (% w/w)	ff_c	Average Particle Size (μm)	Bulk Density (g/ml)
1	1.21	70.6	6.73 ± 0.60	26.9/1.9	0.394 ± 0.002
2	0.71	68.9	7.30 ± 0.20	43.6/2.0	0.513 ± 0.008
3	0.20	68.1	5.70 ± 0.10	44.0/2.2	0.574 ± 0.005
4	2.00	69.7	3.57 ± 0.15	12.5/1.8	0.283 ± 0.002
5	1.60	70.5	6.80 ± 0.10	38.6/2.0	0.442 ± 0.005
6	1.60	69.1	5.67 ± 0.42	35.1/2.0	0.462 ± 0.001
7	1.05	71.0	6.90 ± 0.36	43.6/2.3	0.461 ± 0.002
8	1.10	73.4	7.17 ± 0.06	34.0/1.9	0.407 ± 0.007
9	1.10	70.0	7.23 ± 0.55	38.7/2.1	0.462 ± 0.003
10	4.10	55.8	5.53 ± 0.29	42.8/4.2*	0.450 ± 0.003*
11	1.19	67.6	7.73 ± 0.64	37.5/2.2	0.496 ± 0.002
12	1.70	64.8	7.70 ± 0.79	46.8/2.0	0.535 ± 0.004
13	2.10	71.2	5.90 ± 0.46	43.5/2.1	0.554 ± 0.002
14	1.40	73.7	3.40 ± 0.17	12.6/1.9	0.292 ± 0.003
15	3.20	56.4	4.93 ± 0.21	23.3/4.3	0.352 ± 0.002

*Identified as outlier.
Response results: residual moisture content, process yield, ff_c ($n = 3$, $M \pm SD$); average particle size: D_{50}/span; and bulk density: $n = 3$, $M \pm SD$.

In addition, no significant relationship was obtained for process yield (Table 5). It was already observed previously that the effect of these carbohydrates on the process yield of spray dried drug/carbohydrate mixtures (1:1 ratio) was limited (Gonnissen et al., 2007).

Powder Flowability and Average Particle Size

Flowability index (ff_c) is a measure of the flow properties of spray dried powder mixtures. The average particle size of run 10 was classified as an outlier. Runs 4, 14, and 15 which had a high maltodextrin fraction (23.25% w/w) had a significantly lower flowability index and average particle size compared with formulations with a low maltodextrin fraction (4.65% w/w for runs 2, 3, 7, 11, 12, and 13; Table 5). Since spray drying acetaminophen/carbohydrate solutions (1:1) containing erythritol and mannitol resulted in crystalline nonhygroscopic powders and modulated differential scanning calorimetry experiments showed completely amorphous maltodextrin in its corresponding cospray dried drug/carbohydrate mixture (Gonnissen et al., 2007), the formulations containing a higher maltodextrin fraction are more hygroscopic and more cohesive, resulting in poor powder flowability (Forrester & Boardman, 1986; Vidgren, Vidgren, & Paronen, 1987; Chawla, Taylor, Newton, & Johnson, 1994). Scanning electron microscopy (SEM) pictures (Figure 1) of formulations with increasing maltodextrin content (4.65%, 13.95%, and 23.25% w/w in runs 13, 6, and 4, respectively) showed that the smaller particle size caused a decrease of the powder flowability. At a constant maltodextrin concentration in the spray dried powders, the flowability index was adversely affected by the erythritol content (e.g., run 7 versus 13 at 4.65% w/w maltodextrin), probably because of the formation of oblong powder particles in comparison with the more spherical particle shape of the formulation containing mainly mannitol. SEM pictures of acetaminophen/excipient mixtures (1:1) containing erythritol and mannitol show large oblong particles and more spherical agglomerates, respectively (Gonnissen et al., 2007). At a high maltodextrin fraction (23.25% w/w), a decreasing erythritol concentration resulted in a higher average particle size.

The prediction equations in terms of pseudo components for the flowability index (ff_c) and average particle size (D_{50}) were:

$$ff_c = 7.17*A + 5.80*B - 2.10*C + 4.67*AB + 12.89*AC + 10.54*BC \quad (3)$$

$$(D_{50})^{2.31} = 5629.2*A + 6604.8*B - 3146.8*C \quad (4)$$

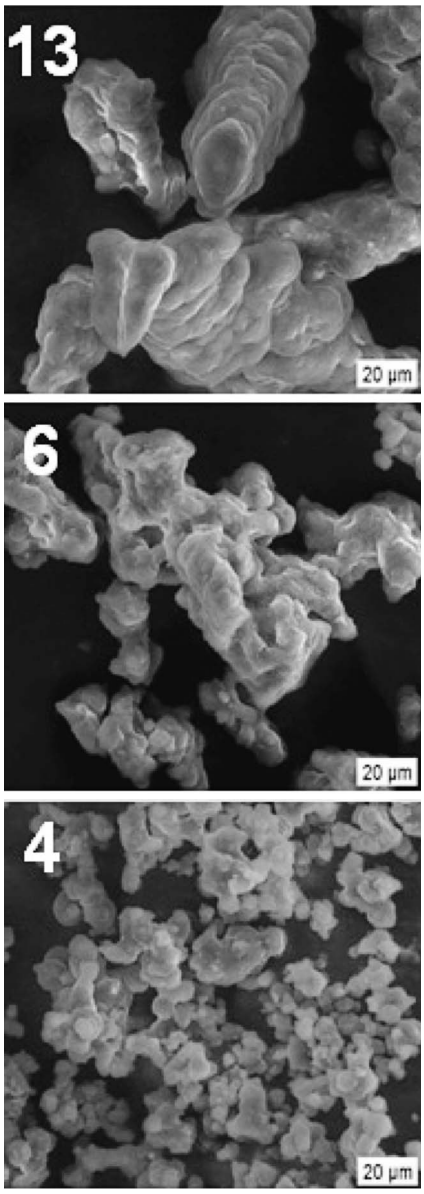

FIGURE 1. SEM pictures of mixture design experiments containing 4.65% w/w (run 13), 13.95% w/w (run 6), and 23.25 % w/w (run 4) maltodextrin.

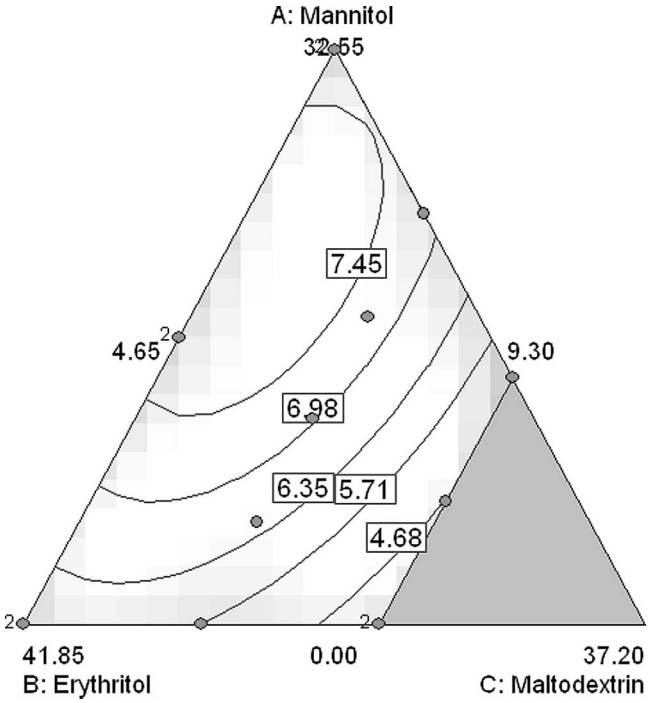

FIGURE 2. Contour plot for flowability.

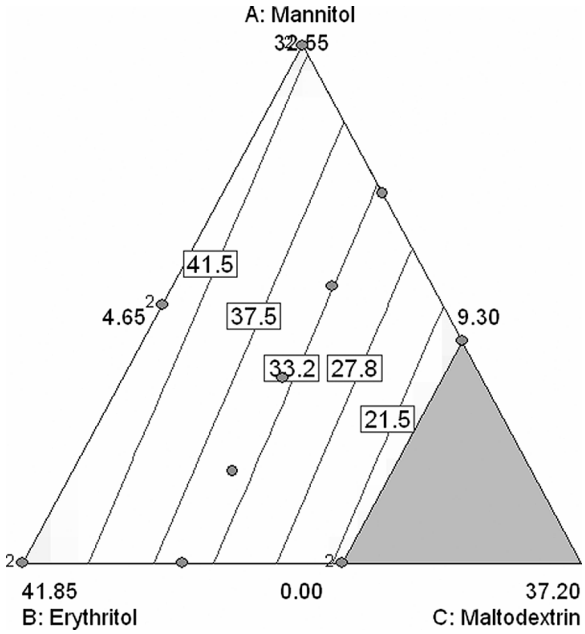

FIGURE 3. Contour plot for average particle size D_{50}.

where A is the relative mannitol fraction, B is the relative erythritol fraction, and C is the relative maltodextrin fraction in the final compact. The contour plots based on Equations 3 and 4 are given in Figures 2 and 3.

Powder Bulk Density

Bulk density of run 10 was classified as an outlier. Runs 2, 3, 11, 12, and 13, containing a low maltodextrin fraction (4.65% w/w), had a significantly higher bulk density in comparison with formulations with a medium (13.95% w/w for runs 1, 5, 6, 8, and 9) and high (23.25% w/w for runs 4, 14, and 15) maltodextrin fraction (Table 5). At a constant maltodextrin content (4.65% or 13.95% w/w), the bulk density increased with higher erythritol content. Similarly, cospray dried acetaminophen/excipient mixtures (1:1) containing erythritol or mannitol had higher bulk densities in comparison with binary mixtures containing maltodextrin (Gonnissen et al., 2007).

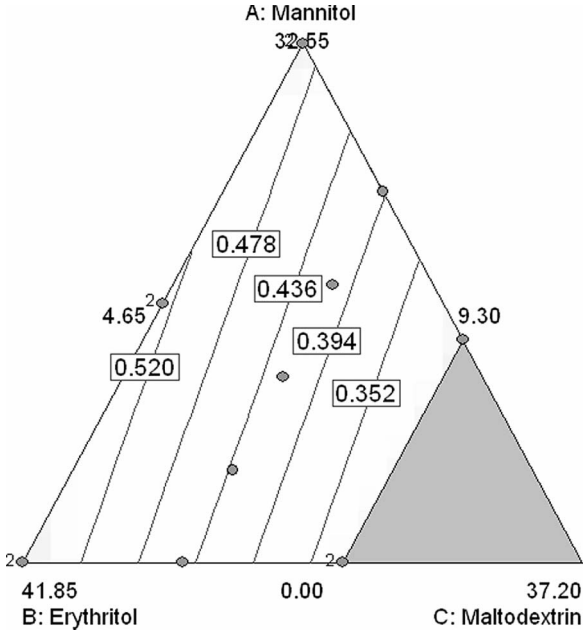

FIGURE 4. Contour plot for bulk density.

The prediction equation in terms of pseudo components for the bulk density (BD) was:

$$BD = 0.490 * A + 0.560 * B + 0.150 * C \quad (5)$$

where A is the relative mannitol fraction, B is the relative erythritol fraction, and C is the relative maltodextrin fraction in the final compact. The contour plot based on Equation 5 is shown in Figure 4.

Powder Hygroscopicity

Water uptake depended on the maltodextrin fraction due to its hygroscopic properties (Table 6). Spray drying acetaminophen/maltodextrin solutions (1:1) resulted in a hygroscopic powder absorbing about 8.5% water at a relative humidity above 50%, while mixtures containing erythritol and mannitol were crystalline and nonhygroscopic powder mixtures (Gonnissen et al., 2007).

Formulations containing a low maltodextrin content (4.65% w/w) had a significantly lower water uptake compared with compositions containing 13.95% or 23.25% w/w maltodextrin. At a constant maltodextrin fraction, the water uptake at 85% relative humidity decreased with higher erythritol contents. At a lower relative humidity, no significant relationship was found between erythritol and mannitol content and the water uptake of the spray dried powders.

The prediction equations in terms of pseudo components for the hygroscopicity (WU) at different relative humidity levels (33% and 85%) were:

TABLE 6
Response Results (Hygroscopicity at 33, 52, 65, 75, and 85% Relative Humidity) for Mixture Design Experiments

	Responses				
	Hygroscopicity				
Run	33% (%)	52% (%)	65% (%)	75% (%)	85% (%)
1	1.60	2.60	2.87	2.81	4.27
2	1.01	1.07	1.18	1.20	1.57
3	0.67	1.02	0.99	0.78	1.12
4	2.48	3.69	3.82	4.50	4.82
5	1.62	2.37	2.11	3.03	3.41
6	1.77	2.50	2.62	2.80	3.11
7	0.90	0.68	0.97	1.31	1.79
8	1.21	2.37	2.49	3.01	3.78
9	0.91	2.21	2.32	2.81	4.03
10	2.11	3.39	3.61	4.83	6.32
11	0.40	1.29	1.08	0.87	1.90
12	0.81	0.89	0.87	1.18	1.57
13	0.39	0.91	0.90	0.98	0.87
14	2.13	3.48	3.47	4.28	5.48
15	1.89	3.58	3.91	4.92	6.43

$$WU(33\%RH) = 0.69 * A + 0.70 * B + 3.24 * C \quad (6)$$

$$WU(85\%RH) = 2.05 * A + 0.93 * B + 9.13 * C \quad (7)$$

where A is the relative mannitol fraction, B is the relative erythritol fraction, and C is the relative maltodextrin fraction in the final compact. The contour plots based on Equations 6 and 7 are shown in Figures 5 and 6, respectively.

Tablet Tensile Strength, Disintegration Time, and Friability

Acetaminophen was used as the model drug because of its poor compactability, as evidenced by the low tablet tensile strength (0.38 MPa and 0.67 MPa at a compression pressure of 74 MPa and 111 MPa, respectively; Gonnissen et al., 2007), as well as capping and lamination problems after compaction of pure spray dried acetaminophen. Tablet friability of run 13 was classified as an outlier. The tensile strength and disintegration time of tablets formulated with low maltodextrin content was significantly lower compared with tablets containing medium or high fractions of maltodextrin, while friability was higher (Table 7). At 4.65% w/w maltodextrin in the spray dried powders, the tablet tensile strength and disintegration time were reduced at higher erythritol contents (41.85% w/w). At higher levels of maltodextrin, no significant relationship was seen

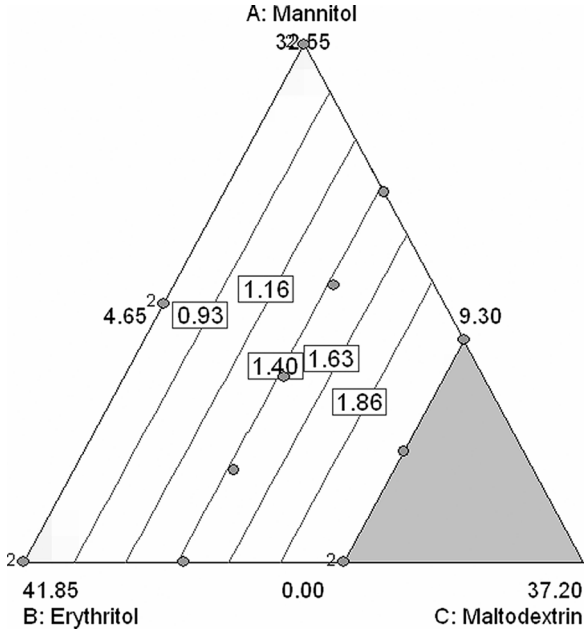

FIGURE 5. Contour plot for hygroscopicity (33% RH).

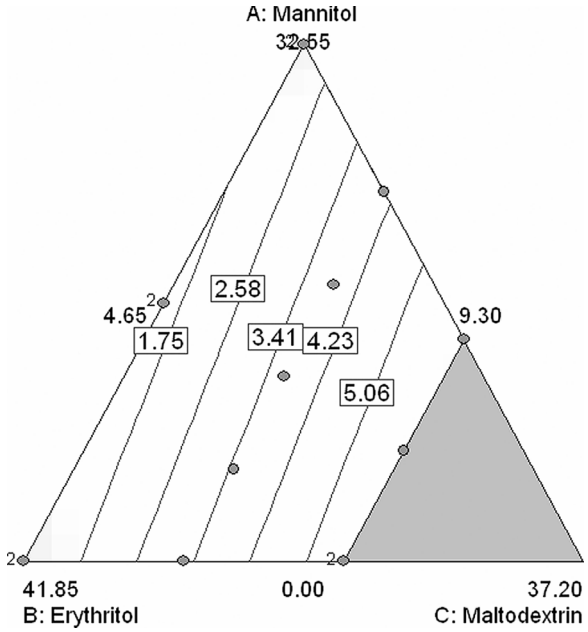

FIGURE 6. Contour plot for hygroscopicity (85% RH).

between the erythritol and mannitol content and the tablet properties.

Mollan and çelik (1993, 1994) state that the slow disintegration of tablets containing high maltodextrin concentrations (25.0–99.5% w/w) was not controlled by the porosity of the tablet, but by a gel layer that formed around the tablet upon immersion into water. Therefore, maltodextrins with identical amylose/amylopectin ratios have similar disintegration behavior independent of the compression pressure.

TABLE 7
Response Results, Tablet Disintegration Time, and Tablet Friability for Mixture Design Experiments

	Responses		
Run	Tablet Tensile Strength (MPa)	Tablet Disintegration Time (s)	Tablet Friability (%)
1	2.13 ± 0.21	453 ± 49	0.87 ± 0.19
2	1.44 ± 0.12	117 ± 14	1.29 ± 0.52
3	1.10 ± 0.07	41 ± 2	1.28 ± 0.16
4	2.75 ± 0.40	843 ± 141	0.60 ± 0.30
5	1.91 ± 0.13	702 ± 201	0.57 ± 0.08
6	2.32 ± 0.17	647 ± 220	0.58 ± 0.17
7	2.03 ± 0.11	86 ± 10	1.03 ± 0.34
8	2.84 ± 0.22	591 ± 2	0.81 ± 0.05
9	2.14 ± 0.18	495 ± 52	0.98 ± 0.17
10	2.91 ± 0.21	1022 ± 290	0.56 ± 0.06
11	1.67 ± 0.21	73 ± 8	1.28 ± 0.27
12	1.43 ± 0.12	72 ± 23	1.68 ± 0.10
13	1.00 ± 0.10	45 ± 12	2.39 ± 0.34*
14	3.09 ± 0.37	776 ± 113	0.78 ± 0.18
15	3.24 ± 0.13	979 ± 218	0.67 ± 015

*Identified as outlier.

Response results: tablet tensile strength (n = 10, $M \pm SD$); tablet disintegration time: (n = 6, $M \pm SD$); and tablet friability: (n = 3, $M \pm SD$).

Compression pressure: 74 MPa.

The prediction equations in terms of pseudo components for the tablet tensile strength (TTS), disintegration time (TDT), and friability (TF) were, respectively:

$$TTS = 1.78 * A + 1.13 * B + 4.24 * C \quad (8)$$

$$\text{Log}_{10}(TDT) = 1.88 * A + 1.65 * B + 1.97 * C + 0.76 * AB + 4.06 * AC + 4.58BC \quad (9)$$

$$TF = 1.22 * A + 1.27 * B + 0.047 * C \quad (10)$$

where A is the relative mannitol fraction, B is the relative erythritol fraction, and C is the relative maltodextrin fraction in the final compact. The contour plots based on Equations 8, 9, and 10 are given in Figures 7, 8, and 9, respectively.

Formulation Optimization and Validation

Numerical optimization was performed using statistical models to find the optimal formulation. For optimization of the

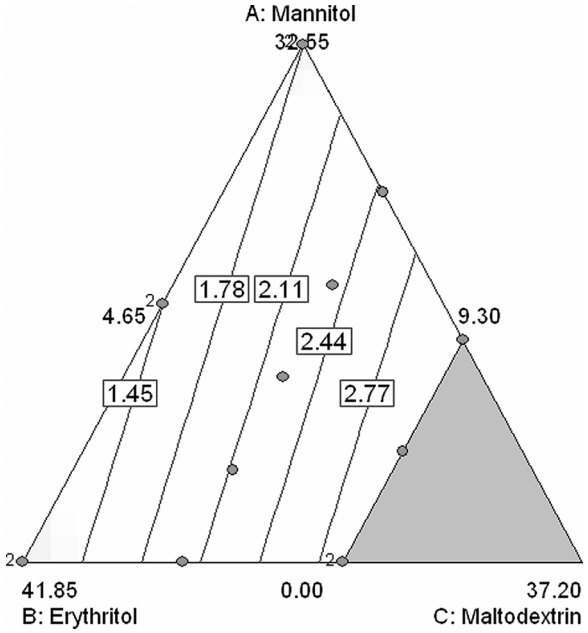

FIGURE 7. Contour plot for tablet tensile strength.

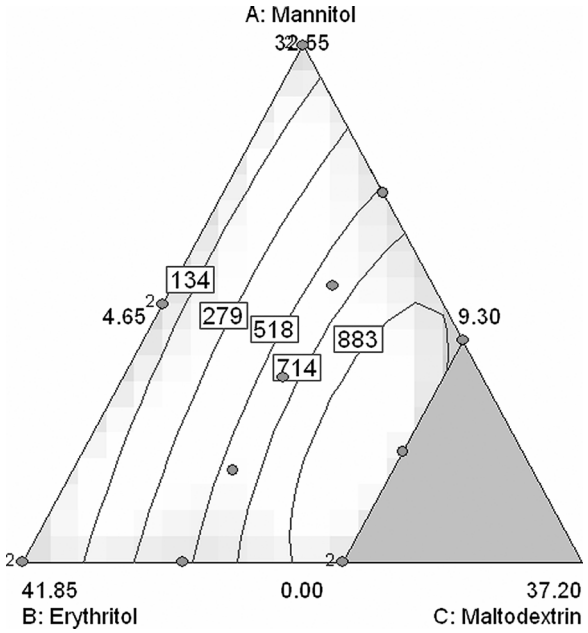

FIGURE 8. Contour plot for tablet disintegration time.

formulation, the following targets were set: the flowability index and density must be higher than 7.0 and 0.400, respectively; and the tablet tensile strength must be maximized while disintegration time and friability must be minimized. According to the statistical prediction, the optimal formulation was:

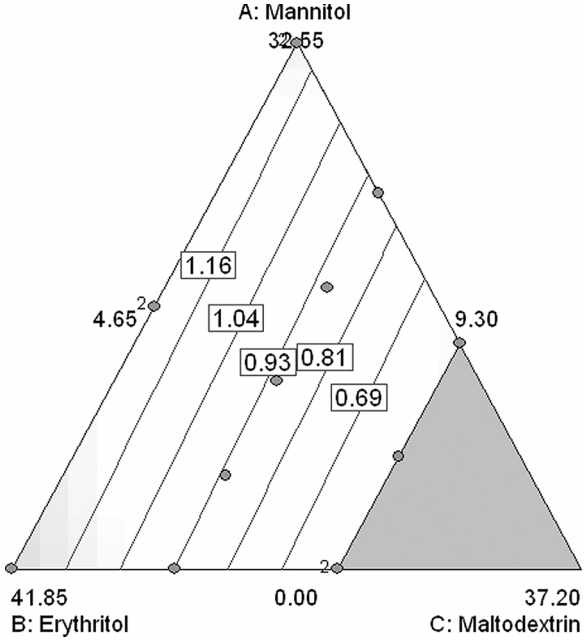

FIGURE 9. Contour plot for tablet friability.

acetaminophen: 46.5% w/w
mannitol: 11.6% w/w
erythritol: 20.9% w/w
maltodextrin: 13.9% w/w

An experiment was performed using the selected mixture to validate the different response models. In addition, point predictions were constructed by entering the optimal content level (% w/w of tablet composition) of each component into the models. The Design-Expert software package (version 6.0.10, Stat-Ease, Minneapolis, USA) then calculated the expected responses and associated confidence and prediction intervals (Table 8) based on the prediction equations (3–10). The prediction interval had a wider spread than the confidence interval since more scatter can be expected in individual values than in averages. All the observed results of the measured responses were within the prediction intervals and in good agreement with the predicted results (Table 8).

CONCLUSIONS

Regression models were developed for powder flowability, average particle size, density, and hygroscopicity. In addition, tablet tensile strength, friability, and disintegration time were modeled, while there was no significant relationship between formulation composition, on the one side, and residual moisture content and process yield, on the other side. Numerical optimization was applied to determine the optimal contents for mannitol (11.6% w/w), erythritol (20.9% w/w), and maltodextrin (13.9% w/w).

TABLE 8
Observed Responses and Point Prediction of the Optimal Formulation

			95% Confidence Interval		95% Prediction Interval	
Response Factor	Observed	Predicted	Low	High	Low	High
Flowability	6.53	7.02	6.45	7.59	5.73	8.31
Average particle size (D_{50}; μm)	37.1	34.1	31.7	36.3	23.3	41.6
Density (g/ml)	0.433	0.421	0.400	0.440	0.350	0.490
Hygroscopicity (33% RH; %)	1.45	1.42	1.26	1.59	0.77	2.08
Hygroscopicity (52% RH; %)	2.52	2.31	2.20	2.42	1.89	2.73
Hygroscopicity (65% RH; %)	2.76	2.40	2.28	2.52	1.93	2.87
Hygroscopicity (75% RH) (%)	2.95	2.86	2.76	2.97	2.44	3.29
Hygroscopicity (85% RH; %)	3.61	3.67	3.46	3.88	2.85	4.49
Tablet tensile strength (MPa)	1.70	2.25	2.11	2.39	1.69	2.80
Tablet disintegration time (s)	412	637	510	797	384	1058
Tablet friability (%)	1.23	0.90	0.77	1.03	0.40	1.40

Mannitol = 11.6% w/w, erythritol = 20.9% w/w, and maltodextrin = 13.9% w/w.

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