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Research paper

Coprocessing via spray drying as a formulation platform to improve the compactability of various drugs

Y. Gonnissen, E. Verhoeven, E. Peeters, J.P. Remon, C. Vervaet *

Laboratory of Pharmaceutical Technology, Ghent University, Gent, Belgium

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Abstract

It was evaluated if coprocessing via spray drying can be used as a formulation platform to improve the compactability of formulations containing drug substance (acetaminophen, ibuprofen, cimetidine) and excipients (carbohydrates, disintegrant, glidant, surfactant). Experimental design was applied to optimise the drug concentration and solid content of the feed suspension. In addition, scaling-up of acetaminophen- and ibuprofen-containing formulations was performed on a production-scale spray dryer. Optimised acetaminophen (drug concentration: 70% w/w), ibuprofen (drug concentration: 75% w/w) and cimetidine (drug concentration: 70% w/w) powders were obtained via co-spray drying of aqueous suspensions with a high solid content of the feed (35% w/w) and the resulting powders were directly compressed. Scaling-up of optimised acetaminophen and ibuprofen formulations was performed successfully, resulting in a robust and reproducible manufacturing process. It can be concluded that a combination of mannitol, erythritol, Glucidex® 9, Kollidon® CL, colloidal silicon dioxide and polyoxyethylene 20 sorbitan monooleate allowed the spray drying of highly dosed drug substances (acetaminophen, ibuprofen, cimetidine) in order to obtain 'ready-to-compress' powder mixtures on lab-scale and production-scale equipment.

Keywords: Co-spray drying; Scaling-up; Continuous processing; Compression; Acetaminophen; Ibuprofen; Cimetidine; Carbohydrates

1. Introduction

Tablets are still the most commonly used dosage form because of the ease of manufacturing, convenience in administration, accurate dosing and excellent stability, and direct compression is the preferred method for the preparation of tablets. However, it has been estimated that less than 20 percent of the active pharmaceutical ingredients can be processed into tablets via direct compression since the majority lack the flow, cohesion or lubricating properties required for direct compression [1]. Therefore, the formulator has to resort to (wet) granulation techniques to obtain drug/excipient agglomerates with suitable properties for compression. This involves several processing steps (dry mixing, granulation, drying), different equipment, numerous written procedures to be followed and extensive downstream testing for powder homogeneity/segregation. In addition, wet granulation is a batch process and scaling-up of this technique is a labour-intensive and time-consuming process.

An alternative method to improve the compactability of drugs could be the coprocessing of drug substance and excipients via spray drying. This technique has already been used to develop excipient mixtures having superior properties (flowability, hygroscopicity, and compactability) compared to the individual excipients or their physical mixtures [2] (e.g., Cellactose®: α-lactose monohydrate and powdered cellulose, Microcelac®: α-lactose monohydrate and microcrystalline cellulose, Prosolv®: microcrystalline cellulose and silicon dioxide). However, this concept has not been extended to the coprocessing of drug and excipient(s) to alter the physical properties of the drug.

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium. Tel.: +32 9 2648054; fax: +32 9 2228236.
E-mail address: Chris.Vervaet@UGent.be (C. Vervaet).

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Improving the compactability of drugs via co-spray drying is an interesting manufacturing technique for the pharmaceutical industry since it uses a one-step process to dry and agglomerate powder, thus obtaining a homogeneous powder which can become free-flowing through process optimisation [3–6]. Using this technique the number of unit operations is reduced, improving production efficiency and reducing costs, especially since spray drying is a technique which can be easily automated and equipped for in-line product analysis. In addition, spray drying can be considered a continuous process, thus reducing time-to-market because of scale-up benefits and better quality (no batch-to-batch variations, clinical trial batches and production batches are manufactured on the same equipment). These features of coprocessing via spray drying offer many obvious economic benefits for a pharmaceutical production facility.

The purpose of this study is to optimise the solid content of the feed suspension used for co-spray drying in order to maximise the drug concentration of the spray dried powder. Experimental design of the spray drying process is applied to optimise the processibility and physico-chemical properties of the spray dried powder (and corresponding tablets) in order to achieve a continuous production process of solid dosage forms containing a poorly compressible drug substance. In addition, scaling-up of acetaminophen and ibuprofen formulations was performed on a production-scale spray dryer and rotary tablet press.

2. Materials and methods

2.1. Materials

Two acetaminophen-grades (median particle size: 15 μm (Atabay, Istanbul, Turkey) and 50 μm (Mallinckrodt Chemical Ltd., Hazelwood, USA)), 2 ibuprofen-grades (median particle size: 25 μm (Knoll Pharmaceuticals, Nottingham, UK) and 50 μm (BASF, Ludwigshafen, Germany)) and cimetidine (median particle size: 11 μm (Fagron, Waregem, Belgium)) were used as model drugs. Micronised acetaminophen, ibuprofen and cimetidine were selected for coprocessing on a lab-scale Mobile Minor spray dryer (GEA NIRO, Copenhagen, Denmark), while coarser grades of acetaminophen and ibuprofen were used for scaling-up on a production-scale SD 28 spray dryer (GEA NIRO, Copenhagen, Denmark). Erythritol (C* Eridex 16955) and mannitol (C* Mannidex 16700) were donated by Cerestar (Mechelen, Belgium). Maltodextrin (Glucidex® 9) was a gift from Roquette (Lestrem, France). Crospovidone (Kollidon® CL) was kindly donated by BASF (Ludwigshafen, Germany). Polyoxyethylene 20 sorbitan monooleate (Polysorbate 80) was purchased from Certa (Braine L'Alleud, Belgium). Colloidal silicon dioxide (Aerosil® 200) was purchased from Federa (Brussels, Belgium).

2.2. Methods

2.2.1. Preparation of the spray dried particles

Aqueous suspensions of drug substance (acetaminophen, ibuprofen, cimetidine), mannitol, erythritol, maltodextrin (Glucidex® 9), crospovidone (Kollidon® CL), colloidal silicon dioxide (Aerosil® 200) and polyoxyethylene 20 sorbitan monooleate (Polysorbate 80) were prepared to optimise the drug concentration and the solid content of the feed suspension. The feed suspensions were spray dried according to the process conditions shown in Table 1. Spray drying of these suspensions was performed in a 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 suspensions were fed to a rotary atomiser at the top of the spray dryer by means of a peristaltic pump, type 520U (Watson Marlow, Cornwall, UK) and a Marprene® tube (inside diameter: 4.8 mm) (Watson Marlow, Cornwall, UK). The spray dryer operated in co-current air flow and the powder is collected using a cyclone.

In addition, aqueous suspensions (total solid content: 35.0% w/w) containing acetaminophen and ibuprofen (Table 2) were processed on production-scale SD 28 spray dryer (GEA NIRO, Copenhagen, Denmark). In comparison with co-spray drying in a lab-scale spray dryer, coarser drug particles were used during scaling-up to obtain maximum flowability and median particle size of the spray dried powder and to minimise the loss of non-agglomerated drug particles discharged with the drying air. The dimensions of the drying chamber were 1.95 m cylindrical height with a diameter of 2.67 m and 60° conical base. In order to improve flowability, density and median particle size of the spray dried powder, the feed suspension containing acetaminophen was fed to a pressure nozzle (type: SDX, Delavan, Illzach, France; nozzle diameter: 1.0, 1.4, 1.6 mm) at the top of the spray dryer by means of a monopump (Netzsch, Waldkraiburg, Germany). Because of insufficient drying with a pressure nozzle (nozzle diameter: 1.0 mm), the ibuprofen formulation was spray dried using a rotary atomiser (type: A-4-150, GEA NIRO, Copenhagen, Denmark). The spray dryer operated in co-current air flow and the powder is collected at the bottom of the drying chamber. Pneumatic hammers are mounted on the

Table 1
Process conditions during spray drying in the Mobile Minor spray dryer (GEA NIRO)

Process parameters	Acetaminophen	Ibuprofen	Cimetidine
Feed rate (kg/h)	2.9–3.7	0.8–1.1	2.8–3.7
Inlet drying air temperature (°C)	220	120	220
Outlet drying air temperature (°C)	80	65	80
Drying gas rate (kg/h)	80	80	80
Atomising air pressure (bar)	6	6	6
Rotary atomiser speed (rpm)	31,000	31,000	31,000

Table 2
Composition of the feed suspension for the coprocessed formulations in a lab-scale spray dryer (Mobile Minor, GEA NIRO) and production-scale spray dryer (SD 28, GEA NIRO) The ratio between the different components is expressed as a percentage of the total amount of solids

	Mobile Minor	SD 28	
	Acetaminophen, ibuprofen and cimetidine formulations	Acetaminophen	Ibuprofen
	Concentration (% of solids content)		
Drug substance	$\text{Concentration}_{\text{Drug}}$	70.0	75.0
Mannitol	$(93 - \text{Concentration}_{\text{Drug}}) * 0.463$	10.9	8.6
Erythritol	$(93 - \text{Concentration}_{\text{Drug}}) * 0.315$	7.4	5.8
Maltodextrin	$(93 - \text{Concentration}_{\text{Drug}}) * 0.221$	5.2	4.1
Crospovidone	6.0	6.0	6.0
Colloidal silicon dioxide	0.5		
Polysorbate 80	0.5	0.5	0.5

cylindrical and conical part of the chamber to remove powder sticking to the chamber wall. The spray drying conditions are listed in Tables 3 and 4.

The spray dried powders were 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 of acetaminophen formulations in the SD 28 spray dryer (GEA NIRO) using a pressure nozzle (type: Delavan SDX)

Process parameters	Experiment number				
	1	2	3	4	5
Nozzle diameter (mm)	1.0	1.4	1.6	1.6	1.4
Nozzle pressure (bar)	13	14	14	6	6
Feed rate (l/h)	46	66	81	60	47
Drying gas rate (kg/h)	2200	2200	2200	2200	2200
Inlet drying air temperature (°C)	150	170	180	160	155
Outlet drying air temperature (°C)	104	107	103	102	105
Median particle size (D_{50}) (μm)	176	203	239	243	264
Density (g/ml)	0.47	0.47	0.44	0.48	0.39
Residual moisture content (%)	0.81	0.67	1.21	6.66	1.69

Table 4
Process conditions during spray drying of ibuprofen formulations in the SD 28 spray dryer (GEA NIRO) using a pressure nozzle (type: Delavan SDX) in test 1 and a rotary atomiser (type: A-4-150) in tests 2, 3, 4 and 5

Process parameters	Experiment number				
	1	2	3	4	5
Nozzle diameter (mm)	1.0	–	–	–	–
Nozzle pressure (bar)	13	–	–	–	–
Rotary atomiser speed (rpm)	–	20,000	20,000	20,000	15,000
Feed rate (l/h)	58	79	79	54	54
Drying gas rate (kg/h)	2200	2200	2200	2200	2200
Inlet drying air temperature (°C)	140	150	135	115	115
Outlet drying air temperature (°C)	92	75	66	65	64
Median particle size (D_{50}) (μm)	[a]	133	101	98	120
Density (g/ml)	[a]	0.39	0.44	0.43	0.43
Residual moisture content (%)	2.70	0.35	0.56	0.46	0.69

[a] Due to extensive material deposition on the surface of the drying chamber, insufficient powder was collected.

Table 5
Design ranges during spray drying in the Mobile Minor spray dryer (GEA NIRO)

Drug	Experimental design ranges	
	Solid content of the feed (% w/w of total feed)	Drug concentration (% w/w of solid content)
Acetaminophen	25–40	45–70
Ibuprofen	25–35	45–75
Cimetidine	25–40	45–70

2.2.2. Experimental design

Preliminary experiments were carried out to establish appropriate ranges for the solid content of the feed suspension and the drug concentration of the spray dried powder (Table 5). The lower limits of the solid content (25% w/w) of the feed and the drug concentration (45% w/w) were chosen to obtain a minimum production capacity. The upper limit (35% to 40% w/w) of the solid content was selected to avoid pumping problems and blocking of the atomisation device due to high viscosity suspensions. Drug concentration of acetaminophen and cimetidine formulations was limited to 70% w/w because of low tablet tensile strength and high friability at higher drug concentrations, whereas poor powder flowability and low bulk density restricted the ibuprofen concentration to 75% w/w. The design runs for the acetaminophen, ibuprofen and cimetidine formulations are listed in Tables 6–8, respectively.

A classical central composite design was applied. Because interactions between the variables were expected, the following quadratic model Eq. (1) was proposed:

$$Y = \beta_0 + \sum_{i=1}^{2} \beta_i X_i + \sum_{i=1}^{1} \sum_{j=i+1}^{2} \beta_{ij} X_i X_j + \sum_{i=1}^{2} \beta_{ii} X_i^2, \qquad (1)$$

where Y is the response, X_i X_j are the set points of the factors 'i' and 'j', respectively, in the mixture and β_0, β_i, β_{ij} and β_{ii} are the coefficients.

The design points were chosen by the software (Design-Expert version 6.0.10, Stat-Ease Inc., Minneapolis, USA). Manual regression was performed. The highest order polynomial, where the additional interaction terms were significant (significance threshold = 0.05), was selected without

Table 6
Design runs of the central composite design experiments and response results (powder flowability: ff_c (n: 3, mean ± SD), bulk density (n: 3, mean ± SD), residual moisture content, process yield and median particle size (D_{50}/span), tablet tensile strength (n: 10, mean ± SD), tablet disintegration time (n: 6, mean ± SD) and tablet friability (n: 3, mean ± SD)) for co-spray dried powders and tablets containing acetaminophen (compression pressure: 130 MPa)

Run	Factors		Responses							
	A: X_1 solid content of the feed (% w/w)	B: X_2 drug concentration (% w/w)	ff_c	Bulk density (g/ml)	Residual moisture content (% w/w)	Process yield (% w/w)	Median particle size (μm)	Tablet tensile strength (MPa)	Tablet disintegration time (s)	Tablet friability (%)
1	32.5	45.0	7.93 ± 0.31	0.361 ± 0.002[a]	0.69	59.9	42.5/2.2	1.36 ± 0.12	352 ± 10	0.90 ± 0.01
2	27.2	66.3	6.30 ± 0.36	0.308 ± 0.004	0.58	76.2	21.6/2.3	0.91 ± 0.12	225 ± 4	1.36 ± 0.24
3	37.8	66.3	6.43 ± 0.35	0.303 ± 0.002	0.50	81.3	26.1/2.1	0.89 ± 0.13	195 ± 3	1.21 ± 0.05
4	32.5	57.5	6.67 ± 0.21	0.315 ± 0.005	0.54	72.7	30.3/2.2	1.02 ± 0.12	256 ± 17	0.82 ± 0.07
5	40.0	57.5	6.80 ± 0.10	0.305 ± 0.001	0.59	69.2	34.9/2.1	1.01 ± 0.08	263 ± 19	0.92 ± 0.04
6	37.8	48.7	7.20 ± 1.13	0.319 ± 0.006	0.59	62.5	44.3/2.1	1.12 ± 0.09	337 ± 13	0.76 ± 0.09
7	32.5	70.0	5.93 ± 0.06	0.313 ± 0.006	0.40	81.9	20.0/2.1	0.84 ± 0.03	177 ± 18	1.40 ± 0.15
8	32.5	57.5	6.73 ± 0.31	0.323 ± 0.006	1.04	75.6	28.6/2.1	1.09 ± 0.07	263 ± 18	0.78 ± 0.07
9	32.5	57.5	7.30 ± 0.46	0.320 ± 0.001	0.69	76.6	28.5/2.0	1.15 ± 0.22	311 ± 7	0.63 ± 0.04
10	25.0	57.5	6.73 ± 0.06	0.311 ± 0.001	1.14	73.1	24.5/2.2	1.25 ± 0.20	405 ± 24	0.76 ± 0.05
11	27.2	48.7	7.03 ± 0.12	0.330 ± 0.005	0.79	62.8	35.0/2.4	1.39 ± 0.15	404 ± 13	0.65 ± 0.15

[a] Identified as outlier.

Table 7
Design runs of the central composite design experiments and response results (powder flowability: ff_c (n: 3, mean ± SD), bulk density (n: 3, mean ± SD), residual moisture content, process yield and median particle size (D_{50}/span), tablet tensile strength (n: 10, mean ± SD), tablet disintegration time (n: 6, mean ± SD) and tablet friability (n: 3, mean ± SD)) for co-spray dried powders and tablets containing ibuprofen (compression pressure: 86 MPa)

Run	Factors		Responses							
	A: X_1 solid content of the feed (% w/w)	B: X_2 drug concentration (% w/w)	ff_c	Bulk density (g/ml)	Residual moisture content (% w/w)	Process yield (% w/w)	Median particle size (μm)	Tablet tensile strength (MPa)	Tablet disintegration time (s)	Tablet friability (%)
1	26.5	49.4	7.90 ± 0.70	0.379 ± 0.002	0.68	65.4	29.6/3.0	1.45 ± 0.07	854 ± 25	0.53 ± 0.02
2	30.0	60.0	6.73 ± 0.21	0.334 ± 0.002	0.31	69.4	24.5/2.5	1.41 ± 0.16	769 ± 14	0.59 ± 0.06
3	30.0	60.0	7.00 ± 0.30	0.338 ± 0.005	0.70	70.2	24.6/2.4	1.41 ± 0.06	808 ± 44	0.48 ± 0.01
4	30.0	45.0	7.50 ± 0.30	0.369 ± 0.001	0.50	65.9	32.2/2.9	1.49 ± 0.07	703 ± 20	0.56 ± 0.05
5	25.0	60.0	6.43 ± 0.21	0.326 ± 0.002	0.68	64.9	23.8/2.5	1.36 ± 0.18	686 ± 12	0.52 ± 0.02
6	33.5	70.6	5.73 ± 0.25	0.296 ± 0.004	0.31	73.2	20.5/2.2	1.45 ± 0.08	568 ± 20	0.55 ± 0.04
7	35.0	60.0	6.67 ± 0.78	0.306 ± 0.010	0.42	74.9	25.8/2.3	1.32 ± 0.06	662 ± 22	0.46 ± 0.01
8	30.0	60.0	6.90 ± 046	0.310 ± 0.001	0.68	68.8	25.0/2.4	1.46 ± 0.07	674 ± 23	0.44 ± 0.11
9	33.5	49.4	7.63 ± 0.12	0.362 ± 0.004	0.63	69.7	32.0/2.7	1.31 ± 0.05	746 ± 19	0.51 ± 0.02
10	30.0	75.0	5.73 ± 0.25	0.296 ± 0.003	0.50	70.4	19.6/2.2	1.23 ± 0.13	563 ± 8	0.47 ± 0.10
11	26.5	70.6	5.80 ± 0.20	0.306 ± 0.001	0.30	65.9	20.9/2.3	1.28 ± 0.19	622 ± 36	0.48 ± 0.02

Table 8
Design runs of the central composite design experiments and response results (powder flowability: ff_c (n: 3, mean ± SD), bulk density (n: 3, mean ± SD), residual moisture content, process yield and median particle size (D_{50}/span), tablet tensile strength (n: 10, mean ± SD), tablet disintegration time (n: 6, mean ± SD) and tablet friability (n: 3, mean ± SD)) for co-spray dried powders and tablets containing cimetidine (compression pressure: 120 MPa)

Run	Factors		Responses						
	A: X_1 solid content of the feed (% w/w)	B: X_2 drug concentration (% w/w)	ff_c	Bulk density (g/ml)	Residual moisture content (% w/w)	Process yield (% w/w)	Median particle size (μm)	Tablet tensile strength (MPa)	Tablet disintegration time (s)	Tablet friability (%)
1	37.8	48.7	7.27 ± 0.35	0.309 ± 0.002	0.59	66.1	52.2/2.1	1.45 ± 0.19	357 ± 3	0.52 ± 0.03
2	32.5	45.0	7.20 ± 0.40	0.322 ± 0.003	0.91	64.9	55.4/2.4	1.73 ± 0.10	375 ± 7	0.47 ± 0.04
3	27.2	48.7	7.23 ± 1.03	0.323 ± 0.001	0.82	60.0	48.4/2.4	1.80 ± 0.08	370 ± 6	0.50 ± 0.05
4	25.0	57.5	7.93 ± 0.31	0.316 ± 0.002	0.92	71.3	38.3/2.2	1.77 ± 0.09	362 ± 10	0.64 ± 0.08
5	32.5	57.5	7.83 ± 0.57	0.307 ± 0.002	0.57	76.0	40.7/2.1	1.64 ± 0.08	348 ± 5	0.62 ± 0.04
6	32.5	70.0	7.07 ± 0.35	0.306 ± 0.005	0.48	82.0	29.4/2.2	1.32 ± 0.16	281 ± 14	0.95 ± 0.08
7	37.8	66.3	7.57 ± 0.29	0.317 ± 0.001	0.72	83.5	33.3/1.9[a]	1.41 ± 0.04	280 ± 10	0.81 ± 0.05
8	32.5	57.5	7.27 ± 0.29	0.297 ± 0.001	0.38	76.1	40.7/2.1	1.58 ± 0.13	327 ± 16	0.60 ± 0.05
9	32.5	57.5	7.27 ± 0.87	0.301 ± 0.002	0.32	70.0	40.4/2.1	1.51 ± 0.17	320 ± 9	0.56 ± 0.03
10	27.2	66.3	7.10 ± 0.36	0.304 ± 0.007	0.39	79.7	31.2/2.2	1.41 ± 0.07	330 ± 6	0.93 ± 0.07
11	40.0	57.5	7.43 ± 0.29	0.295 ± 0.000	0.50	73.3	44.0/2.0	1.35 ± 0.07	323 ± 5	0.67 ± 0.03

[a] Identified as outlier.

destroying the model hierarchy. 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 a similar correlation after ignoring the insignificant model terms, should have good agreement with predicted R^2 for the model to be fit [7]. Predicted and adjusted R-squares should be within 0.20 of each other [8]. Contour plots for the response were drawn for determination of the optimal variable settings.

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

2.2.3. Spray dried powder evaluation

The flowability (n: 3) (expressed as the flowability index ff_cin Eq. (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 [9]. 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.

$$ff_c = \sigma_1/\sigma_c, \tag{2}$$

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

The median particle size (D_{50}) 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 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 sample of 1.5 g was dried at 105 (acetaminophen, cimetidine) or 70 °C (ibuprofen) during 15 min.

SEM images were recorded with a Quanta 200 FEG (FEI, Eindhoven, The Netherlands) scanning electron microscope. The powder was deposited onto a carbon carrier substrate.

The thermal behaviour of the optimised spray dried mixtures was investigated 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: −20–

200 °C) were performed using a DSC 2920 calorimeter (TA Instrument, New Castle, USA) with a DSC refrigerated cooling system (TA Instruments, New Castle, USA).

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

The superdisintegrant concentration (*n*: 5) in the co-spray dried powders containing acetaminophen and ibuprofen produced on a production-scale spray dryer was gravimetrically determined via a filtration procedure. A powder sample (1.5 g) containing acetaminophen was dispersed in 100 ml demineralised water, while spray dried powder (0.5 g) containing ibuprofen was dispersed in 300 ml phosphate buffer KH_2PO_4 (pH 7.2). 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 prior to use these filters were oven-dried (40 °C) for 2 h. After filtration the glass fiber filters were dried at 40 °C for 72 h and the amount of superdisintegrant retained by the filters was gravimetrically determined.

2.2.4. Tabletting process and evaluation

The powder mixtures produced on a lab-scale spray dryer were compacted on an excentric tablet press, Type EKO (Korsch, Berlin, Germany) equipped with 13.5 mm circular edged punches (tablet weight: 500 ± 5 mg). The tablet properties were evaluated at a compression pressure of 130 (acetaminophen), 86 (ibuprofen) and 120 MPa (cimetidine). The powders produced on a production-scale spray dryer were also compacted on an excentric tablet press at the same compression pressure to compare their dissolution behaviour. Spray dried powders containing cimetidine were blended with 2.0% w/w magnesium stearate for 5 min prior to compression in order to avoid lubrication problems.

The spray dried powders prepared on a production-scale spray dryer were compacted on a rotary Modul™ P tablet press (Courtoy, Halle, Belgium) equipped with 7 mm circular convex punches (tablet weight: 100 ± 2.5 mg). The powders were compacted according to the process conditions shown in Table 9.

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 (*n*: 10) was calculated according to Fell and Newton [10]. 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 ± 0.5 °C). Tablet friability was tested on 10 (500 ± 5 mg) or 20 (100 ± 2.5 mg) tablets (*n*: 3) using a friabilator, Type PTF (Pharma Test, Hainburg, Germany).

Table 9
Process conditions and tablet properties after tablet manufacturing of acetaminophen and ibuprofen spray dried powders on the rotary Modul™ P tablet press (GEA Courtoy)

	Acetaminophen	Ibuprofen
Process parameters		
Production speed (tablets/min)	250	650
$Feeder_1$ speed (rpm)	20	60
$Feeder_2$ speed (rpm)	30	72
Fill depth (mm)	5.04	5.10
Pre-compression force (kN)	8.97	/
Main measured compression force (kN)	11.05	18.96
Tablet properties		
Tablet tensile strength (MPa)	1.08 ± 0.14	0.92 ± 0.03
Tablet disintegration time (s)	269 ± 58	376 ± 31
Tablet friability (%)	0.85 ± 0.12	0.82 ± 0.08

2.2.5. In vitro drug release

The tablets manufactured on the excentric tablet press were introduced in a basket (USP 27, dissolution apparatus 1). The dissolution was performed in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA). Demineralised water was used as dissolution medium for formulations containing acetaminophen and cimetidine, while dissolution of ibuprofen-containing formulations was performed in phosphate buffer KH_2PO_4 (pH 7.2). The temperature of the medium (900 ml) was kept at 37 ± 0.5 °C, while the rotational speed of the baskets was set at 100 rpm. Samples of 5 ml were withdrawn at 5, 10, 15, 30, 45, 60, 75, 90, 120 min and spectrophotometrically analysed for acetaminophen (243 nm), ibuprofen (221 nm) and cimetidine (219 nm) concentration by means of a Perkin-Elmer Lambda 12 UV–VIS double beam spectrophotometer (Zaventem, Belgium). The dissolution was simultaneously performed in six dissolution vessels, each vessel containing one tablet.

3. Results and discussion

3.1. Co-spray drying on a lab-scale spray dryer

3.1.1. Summary statistics for the 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), daily changes of ambient humidity conditions could affect the residual moisture content in the spray dried powder (Tables 6–8) [11]. As a result, the models estimating residual moisture content of spray dried powder mixtures containing acetaminophen, ibuprofen and cimetidine were not significant.

Analysis of variance of the responses (Table 10) indicated that for the optimisation of the acetaminophen formulation response, surface models developed for powder

Table 10
ANOVA – influence of solid content of the feed and acetaminophen concentration on the response factors

Response factor	Model *F*-value	Prob > *F*	Lack-of-fit *F*-value	Prob > *F*
Flowability	37.46	0.0002	0.38	0.8599
Median particle size (D_{50}) (μm)	266.90	< 0.0001	1.03	0.5681
Density (g/ml)	14.61	0.0036	0.68	0.6666
Spray drying yield (%)	68.27	< 0.0001	2.02	0.3711
Tablet tensile strength (MPa)	59.64	< 0.0001	0.20	0.9342
Tablet disintegration time (s)	20.88	0.0007	1.50	0.4522
Tablet friability (%)	29.52	0.0002	1.15	0.5354
	SD	R^2	Adjusted R^2	Predicted R^2
Flowability	0.25	0.8063	0.7847	0.6924
Median particle size (D_{50}) (μm)	0.015	0.9852	0.9815	0.9717
Density (g/ml)	3.589 E-003	0.8796	0.8194	0.6883
Spray drying yield (%)	2.71	0.8835	0.8706	0.8400
Tablet tensile strength (MPa)	0.043	0.9624	0.9462	0.9277
Tablet disintegration time (s)	35.11	0.8392	0.7990	0.6710
Tablet friability (%)	0.11	0.8807	0.8508	0.7281

flowability, median particle size, bulk density, process yield, tablet tensile strength, disintegration time and friability were significant, without significant lack of fit. Transformation of median particle size (logarithmic transformation) was needed because the residuals were a function of the magnitude of the predicted values. In addition, the model summary statistics for the selected significant models were detailed (Table 10). It can be observed that for powder flowability, median particle size, bulk density, process yield, tablet tensile strength, disintegration time and friability, R^2, predicted R^2 and adjusted R^2 were in good agreement, resulting in reliable models.

Reliable and adequate regression models (Table 11) were developed for powder flowability, median particle size, bulk density and process yield of spray dried powders containing ibuprofen. Although the response surface model for tablet disintegration time was significant, R^2, predicted R^2 and adjusted R^2 were not in good agreement. Thus, the developed regression models for tablet tensile strength (not significant), disintegration time (not significant) and friability did not show acceptable statistical measures. Moreover, tablet tensile strength, friability and disintegration time of all design runs were within acceptable ranges (>1.23 MPa, <0.59% and <15 min, respectively) (Table 7).

In addition, median particle size, spray drying yield, tablet tensile strength, disintegration time and friability of spray dried powders composed of cimetidine could be modelled, whereas no significant relationship was discovered between solid content of the feed suspension and cimetidine concentration of the spray dried powder on the one side and flowability index and bulk density on the other side (Table 12).

3.1.2. Combined effect of solid content of the feed and drug concentration

The prediction equations of the developed response surface models in function of the solid content of the feed suspension and the drug (acetaminophen, ibuprofen, cimetidine) concentration are mentioned in Table 13, while the corresponding contour plots are given in Figs. 1–3.

At a constant solid content of the feed suspension, the median particle size of the spray dried powders was negatively affected by the acetaminophen concentration (e.g., run 2 vs 11 and run 3 vs 6 at a solid content of the feed of 27.2% and 37.8% w/w, respectively) (Table 6) as there is less mannitol and maltodextrin available in the formulation to agglomerate the suspended acetaminophen particles. At a constant acetaminophen concentration, the

Table 11
ANOVA – influence of solid content of the feed and ibuprofen concentration on the response factors

Response factor	Model *F*-value	Prob > *F*	Lack-of-fit *F*-value	Prob > *F*
Flowability	87.18	< 0.0001	3.90	0.2193
Median particle size (D_{50}) (μm)	744.67	<0.0001	0.43	0.7558
Density (g/ml)	42.17	0.0001	0.69	0.7029
Spray drying yield (%)	41.45	<0.0001	2.99	0.2720
Tablet disintegration time (s)	10.28	0.0107	0.93	0.6080
	SD	R^2	Adjusted R^2	Predicted R^2
Flowability	0.25	0.9064	0.8960	0.8425
Median particle size (D_{50}) (μm)	0.21	0.9983	0.9970	0.9884
Density (g/ml)	0.013	0.8241	0.8046	0.7541
Spray drying yield (%)	1.08	0.9120	0.8900	0.8149
Tablet disintegration time (s)	67.06	0.5331	0.4812	0.2514

Table 12
ANOVA – influence of solid content of the feed and cimetidine concentration on the response factors

Response factor	Model F-value	Prob > F	Lack-of-fit F-value	Prob > F
Median particle size (D_{50}) (μm)	1198.10	<0.0001	8.16	0.1121
Spray drying yield (%)	53.15	<0.0001	0.64	0.7230
Tablet tensile strength (MPa)	24.24	0.0005	0.83	0.6276
Tablet disintegration time (s)	36.77	<0.0001	0.48	0.7931
Tablet friability (%)	64.77	<0.0001	2.54	0.3094
	SD	R^2	Adjusted R^2	Predicted R^2
Median particle size (D_{50}) (μm)	0.42	0.9983	0.9975	0.9920
Spray drying yield (%)	2.97	0.8552	0.8391	0.7743
Tablet tensile strength (MPa)	0.061	0.9122	0.8746	0.7466
Tablet disintegration time (s)	11.40	0.9019	0.8774	0.8195
Tablet friability (%)	0.045	0.9418	0.9273	0.8979

Table 13
Prediction equations in terms of coded factors for reliable and adequate regression models (A, solid content of the feed suspension; B, drug concentration)

Acetaminophen
Flowability $= 6.82 - 0.54 * B$
Log_{10} (median particle size (D_{50})) $= 1.47 + 0.05 * A - 0.11 * B$
Density $= 0.32 - 3.061\text{E-}003 * A - 8.180\text{E-}003 * B - 6.224\text{E-}003 * A^2$
Spray drying yield $= 71.98 + 7.92 * B$
Tablet tensile strength $= 1.09 - 0.08 * A - 0.18 * B + 0.06 * AB$
Tablet disintegration time $= 290 - 37 * A - 71 * B$
Tablet friability $= 0.79 + 0.23 * B + 0.19 * B^2$

Ibuprofen
Flowability $= 6.73 - 0.81 * B$
Median particle size (D_{50}) $= 24.74 + 0.61 * A - 5.04 * B + 1.00 * B^2 - 0.71 * AB$
Density $= 0.33 - 0.03 * B$
Spray drying yield $= 68.98 + 3.22 * A + 1.30 * B$

Cimetidine
Median particle size (D_{50}) $= 40.81 + 1.90 * A - 8.95 * B + 0.79 * B^2$
Spray drying yield $= 72.99 + 7.66 * B$
Tablet tensile strength $= 1.54 - 0.12 * A - 0.13 * B + 0.087 * AB$
Tablet disintegration time $= 334 - 15 * A - 31 * B$
Tablet friability $= 0.62 + 0.17 * B + 0.051 * B^2$

median particle size increased with the solid content of the feed suspension (e.g., runs 10, 8 and 5 at a solid content of the feed suspension of 25.0%, 32.5% and 40.0% w/w, respectively) due to the larger volume occupied by the solid fraction, resulting in more particle collisions and agglomeration. In addition, a higher solid content of the feed suspension increased the viscosity of the feed, forming larger droplets. Identical observations were made for ibuprofen and cimetidine formulations (Table 7, 8). Similarly, Gonnissen et al. [6] measured a higher median particle size at higher solid content of the feed suspension, while Al-Asheh et al. [12] showed an increased median particle size at increasing solid content of the feed suspension during the production of tomato powder from tomato paste.

Formulations with a high acetaminophen concentration resulted in a lower bulk density of the spray dried powder, probably caused by the large fraction of non-agglomerated acetaminophen particles having a low bulk density ($\rho_{\text{pure micronised acetaminophen}}$: 0.228 g/ml) due to their cohesive and fluffy nature. Although an increasing solid content of the feed normally results in a higher bulk density [10], the specific quadratic relationship between solid content of the feed suspension and bulk density (Table 13) resulted in an optimal bulk density (ρ: 0.321 g/ml) at a solid content of 31.2% w/w (e.g., runs 10, 5 vs runs 4, 8, 9 at an acetaminophen concentration of 57.5% w/w) (Table 6). At higher solid content of the feed suspension, the fraction solid material remaining in suspension (mainly the acetaminophen particles since mannitol, erythritol and maltodextrin dissolved in water) was higher, yielding more non-agglomerated acetaminophen particles and resulting in a lower bulk density. In contrast to acetaminophen-containing particles, the bulk density of ibuprofen formulations only depended on the drug concentration (Table 7).

At a constant solid content of the feed suspension, runs 1, 11 with a low acetaminophen concentration (45.0% and 48.7% w/w, respectively) had a significantly higher tablet tensile strength and disintegration time compared with highly dosed formulations (70.0% w/w for run 7% and 66.3% w/w for run 2) (Table 6). At higher acetaminophen

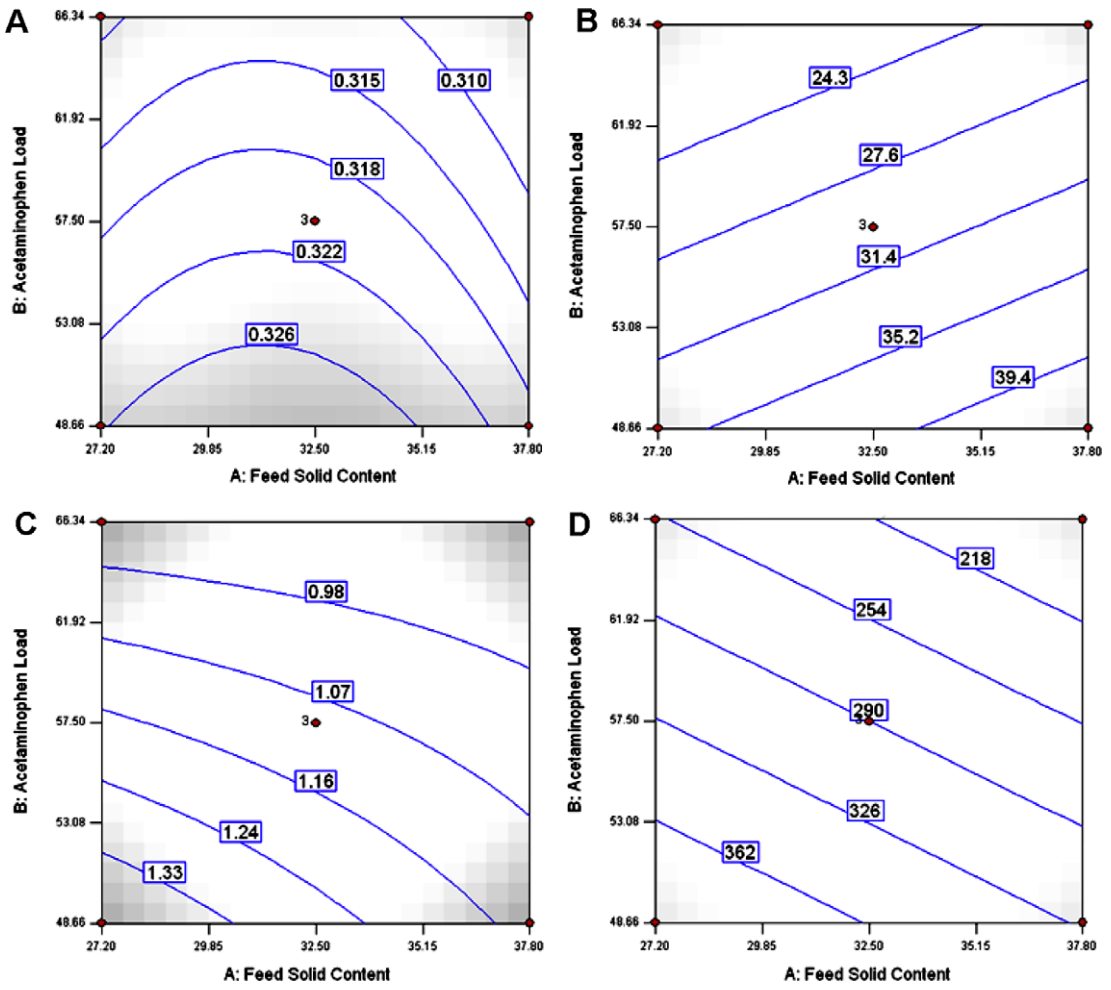

Fig. 1. Influence of solid content of the feed suspension and acetaminophen concentration on density (A), median particle size (B), tablet tensile strength (C) and tablet disintegration time (D).

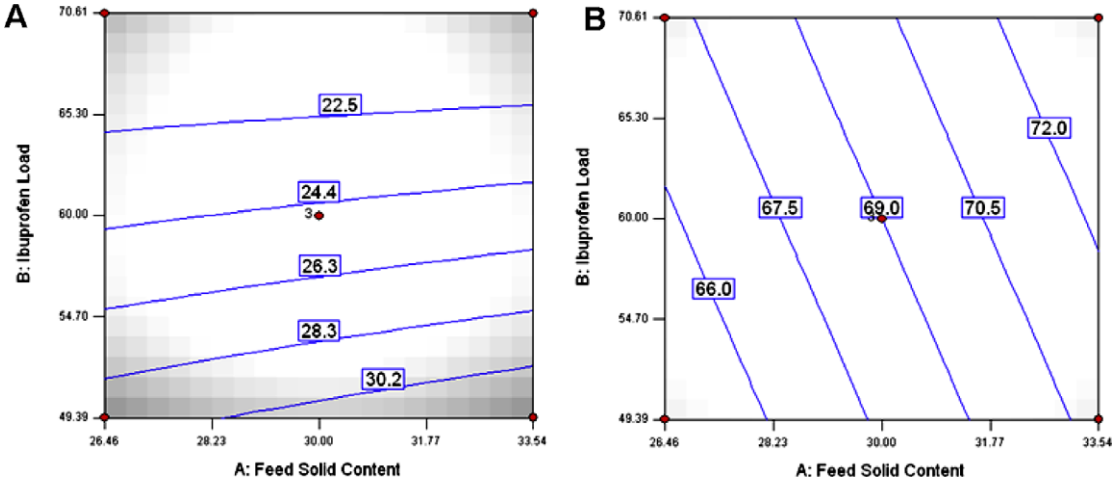

Fig. 2. Influence of solid content of the feed suspension and ibuprofen concentration on median particle size (A) and process yield (B).

concentration, less binder (mannitol, maltodextrin) is available and weaker tablets are produced because of the poor compactability of acetaminophen. In addition, the solid content of the feed decreased tablet tensile strength and disintegration time (e.g., runs 10, 8 and 5 at a solid concentration of 25.0%, 32.5% and 40.0% w/w, respectively).

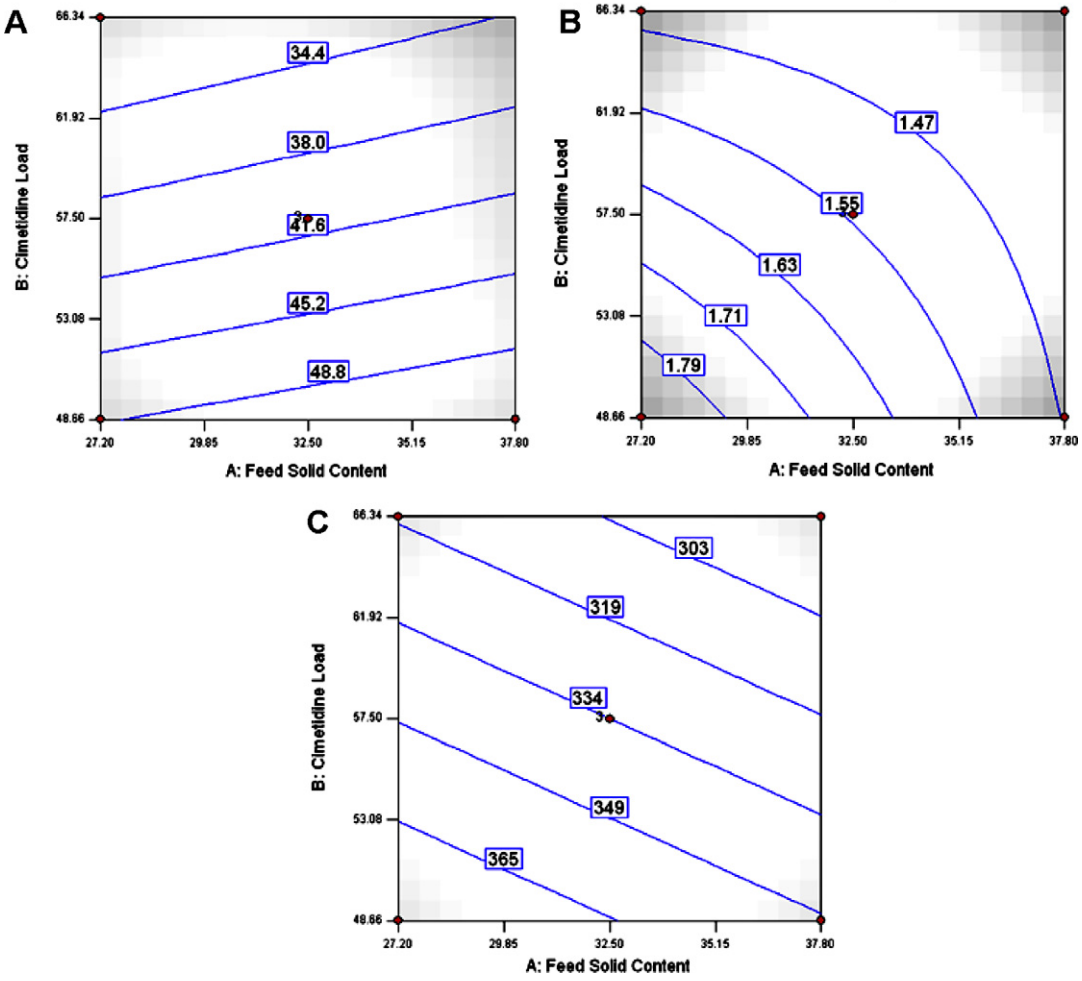

Fig. 3. Influence of solid content of the feed suspension and cimetidine concentration on median particle size (A), tablet tensile strength (B) and tablet disintegration time (C).

Similarly, Gonnissen et al. [6] stated a lower tablet tensile strength and disintegration time at higher solid content of the feed suspension. Identical observations were made for the cimetidine formulation (Table 8), while tablet tensile strength and disintegration time of ibuprofen formulations were independent of the solid content of the feed suspension and drug concentration.

3.1.3. Effect of drug concentration

The prediction equations for the developed response surface models in function of the drug (acetaminophen, ibuprofen, cimetidine) concentration are mentioned in Table 13, while the corresponding contour plots are given in Figs. 4–6.

Formulations containing a high acetaminophen content (66.3% w/w for runs 2%, 3% and 70% w/w for run 7) had a significantly higher process yield and tablet friability compared to compositions containing less drug substance (45% w/w for run 1% and 48.7% w/w for runs 6, 11) (Table 6), while the solid content of the feed suspension had no significant influence on the process yield and tablet friability. At higher acetaminophen concentration, the fraction solid material remaining in suspension (mainly drug substance since mannitol, erythritol and maltodextrin dissolved in water) increased and because it is easier to achieve moisture removal from suspensions-type droplets than solution-type droplets (especially when the latter involves diffusion-limited film-forming characteristics at the surface [11]), process yield improved. In addition, tablet friability increased at higher acetaminophen concentration: the lower content of binding material (mannitol, maltodextrin) weakened the tablets. Similar observations were made for cimetidine formulations (Table 8). The process yield of ibuprofen formulations was also determined by the solid content of the feed suspension.

Runs 2, 3, 7 with a high acetaminophen concentration (66.3–70.0% w/w) had a significantly lower flowability index compared with low dosed formulations (48.7% w/w for runs 6%, 11% and 45% w/w for run 1) (Table 6). The solid content of the feed had no influence on the flowability index. Since a higher drug concentration resulted in smaller spray dried particles having a lower bulk density, the flowability index was negatively influenced. Similar observations were made for ibuprofen formulations (Table 7).

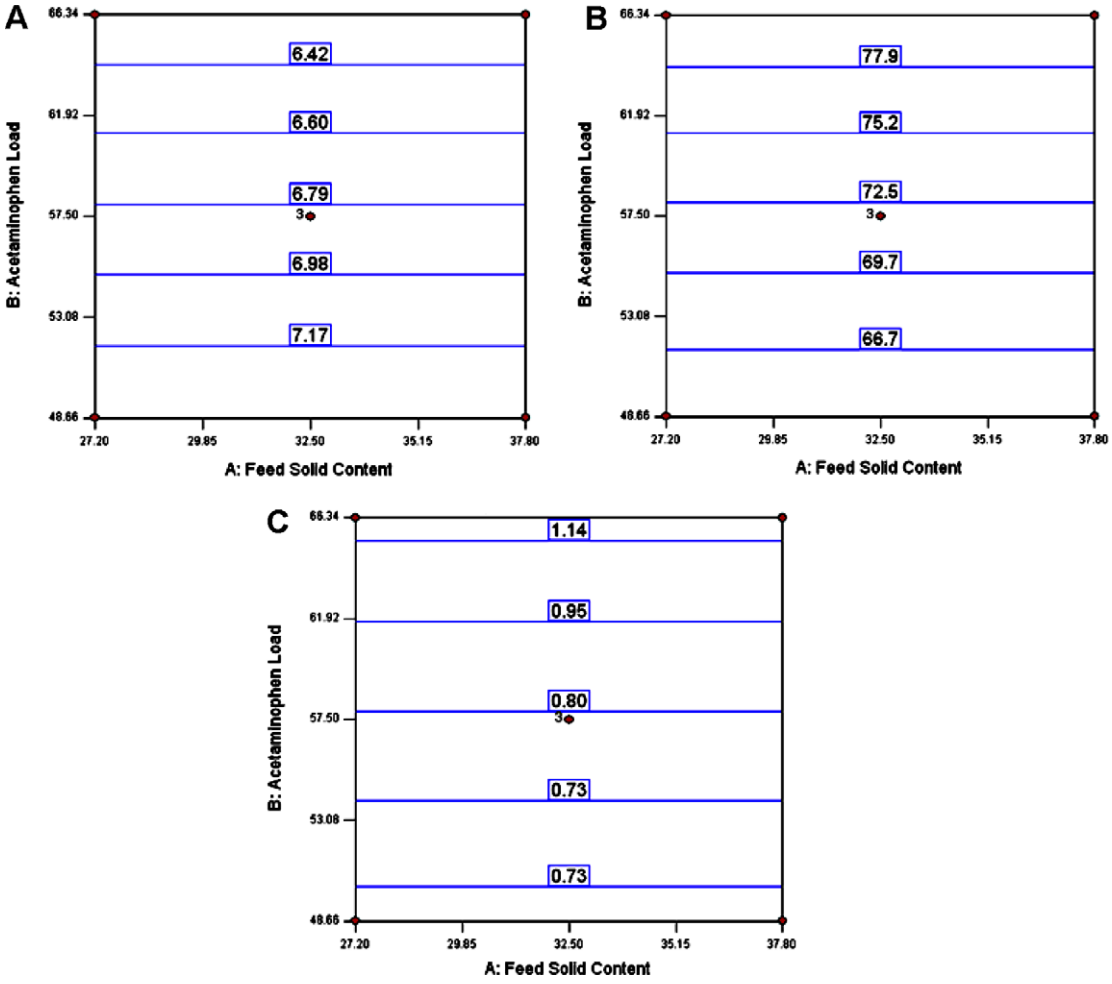

Fig. 4. Influence of acetaminophen concentration on flowability (A), process yield (B) and tablet friability (C).

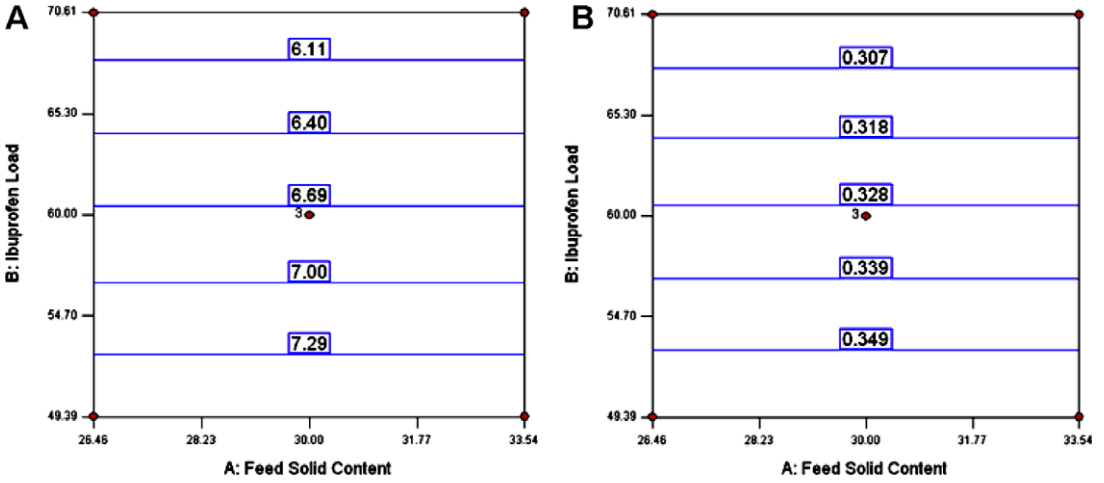

Fig. 5. Influence of ibuprofen concentration on flowability (A) and density (B).

3.2. Co-spray drying on a production-scale spray dryer

3.2.1. Scaling-up of acetaminophen formulation

Numerical optimisation was performed using statistical models (Table 13) to find the optimal solid content of the feed suspension (35.0% w/w) and drug concentration (70% w/w) for coprocessing on a production-scale spray dryer. Different experimental conditions were studied (Table 3). Spray dried powder produced using experiment 2 (nozzle diameter: 1.4 mm, inlet drying air temperature:

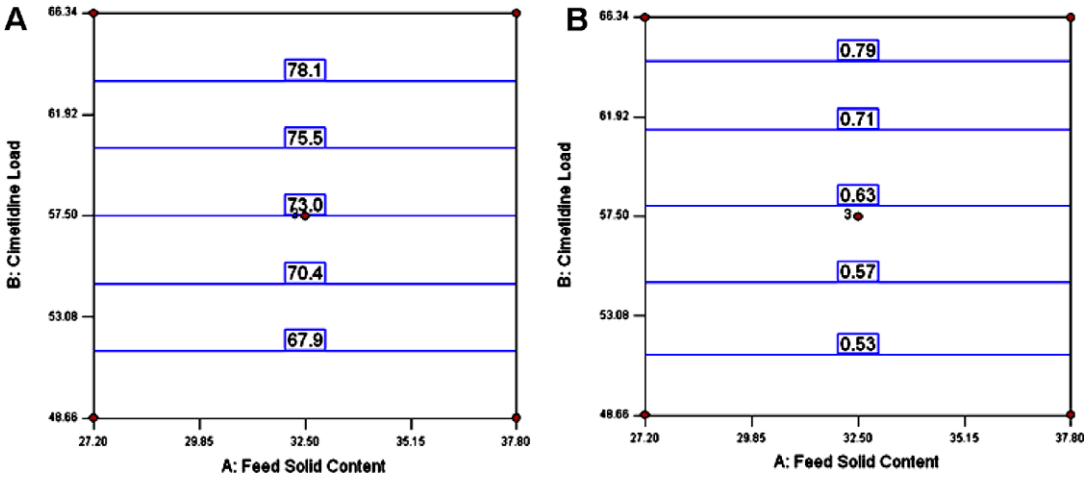

Fig. 6. Influence of cimetidine concentration on process yield (A) and tablet friability (B).

170 °C, outlet drying air temperature: 107 °C) was selected for further characterisation and tablet production, because of its excellent median particle size (203 μm), powder flowability (ff_c: 11.67 ± 0.58) and bulk density (ρ_{bulk}: 0.464 ± 0.006 g/ml) without the formation of deposits on the surface inside the drying chamber. Co-spray drying using a 1.0 mm pressure nozzle (Experiment 1) resulted in a powder mixture with a median particle size of 176 μm because of the lower feed rate, yielding smaller droplets which dried too fast to allow particle agglomeration. Although the median particle size increased up to 239 (Experiment 3), 243 (Experiment 4) and 264 μm (Experiment 5), deposits were formed on the surface of the drying chamber because of the larger diameter of nozzle and/or the low nozzle pressure.

During tablet production on a rotary Modul™ P tablet press, different process conditions (production speed, feeder speed, pre-compression and compression force) were tested, resulting in an optimised tablet production process using a pre-compression force of 8.97 kN (Table 9). Tablet tensile strength, disintegration time and friability were within acceptable ranges: 1.08 ± 0.14 MPa, 269 ± 58 s, $0.85 \pm 0.12\%$, respectively (Table 9).

3.2.2. Scaling-up of ibuprofen formulation

Similarly, numerical optimisation was performed using statistical models (Table 13) to find the optimal solid content of the feed suspension (35.0% w/w) and drug concentration (75% w/w) for coprocessing on a production-scale spray dryer. Different sets of experimental conditions were studied (Table 4). During Experiment 1 the concentrated feed was fed to a pressure nozzle (nozzle diameter: 1 mm), but no powder was collected due to extensive material deposition on the surface of the drying chamber. Therefore, a rotary atomiser (speed: 15,000–20,000 rpm) was used for further experiments. Agglomerated powder manufactured using Experiment 2 was selected for further characterisation and tablet production due to its excellent powder flowability (ff_c: 9.27 ± 0.78) and high bulk density (ρ_{bulk}: 0.391 ± 0.004 g/ml). Reducing the drying temperatures (Experiments 3 and 4) to 136–115 and 66–65 °C resulted in smaller spray dried particles (median particle size: ±100 μm). A reduction of the rotary atomiser speed to 15,000 rpm (Experiment 5) increased the median particle size (120 μm). Nevertheless, spray dried powders produced using process parameters in tests 3, 4 and 5 showed poor powder flowability.

During tablet production on a rotary Modul™ P tablet press, different process conditions (production speed, feeder speed, pre-compression and compression force) were tested, resulting in an optimised tablet production process shown in Table 9. Tablet tensile strength, disintegration time and friability were within acceptable ranges:

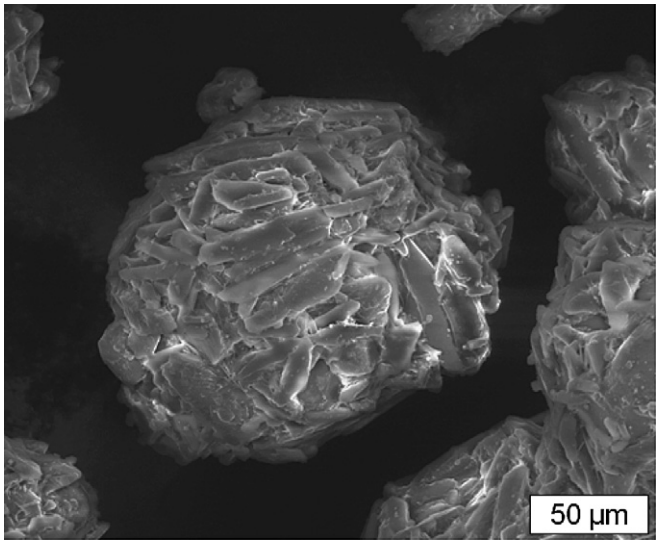

Fig. 7. SEM picture of acetaminophen formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 70% w/w).

0.92 ± 0.03 MPa, 376 ± 31 s, $0.82 \pm 0.08\%$, respectively (Table 9).

3.3. Physico-chemical properties of the optimised formulations

SEM pictures of the powder mixtures containing acetaminophen (Fig. 7) and ibuprofen (Fig. 8) processed on a production-scale spray dryer using optimal process conditions showed spherical agglomerates containing acetaminophen, while the ibuprofen formulation resulted in irregular agglomerates.

After lab-scale production of powder mixtures containing cimetidine, SEM pictures (Fig. 9) showed irregular agglomerates with a lower powder flowability (ff_c: 7.07 ± 0.35) and bulk density (ρ_{bulk}: 0.306 ± 0.005 g/ml) compared with acetaminophen and ibuprofen formulations, mainly caused by the lower median particle size and manufacturing on a lab-scale spray dryer of the cimetidine formulation.

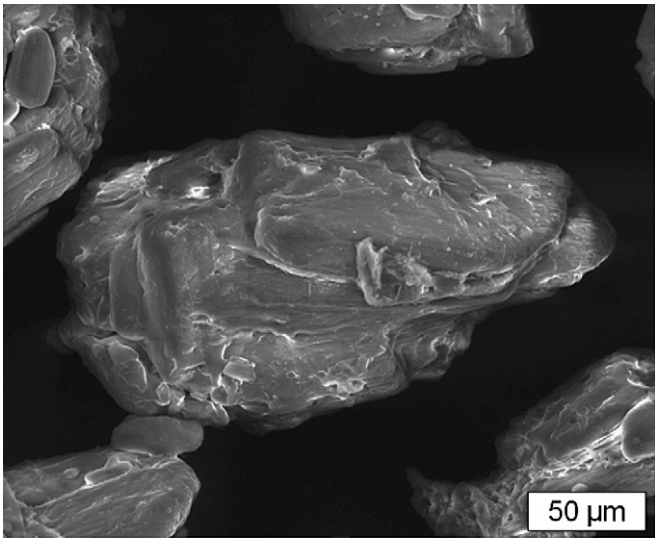

Fig. 8. SEM picture of ibuprofen formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 75% w/w).

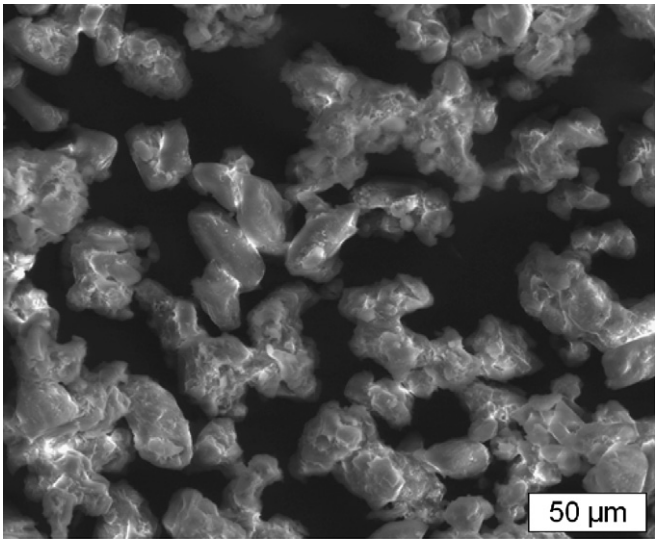

Fig. 9. SEM picture of cimetidine formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 70% w/w).

Modulated DSC experiments of the optimised spray dried mixtures identified crystalline drug substance (acetaminophen, ibuprofen, cimetidine), mannitol and erythritol.

In addition, Fig. 10 showed the X-ray diffraction spectra of the selected spray dried powders containing acetaminophen (top), ibuprofen (middle) and cimetidine (bottom). Acetaminophen, ibuprofen and cimetidine in the spray dried powder mixture were of crystalline nature as sharp peaks were observed in the diffraction pattern. Erythritol and mannitol were crystalline as identified by their prominent peaks in the diffraction spectra, while maltodextrin was amorphous.

Dissolution results on tablets produced from the acetaminophen and ibuprofen powder mixtures manufactured on a lab-scale and production-scale spray dryer were compared. Tablets containing spray dried particles produced on a production-scale spray dryer had a faster drug dissolution caused by a faster tablet disintegration. Gonnissen et al. [3] reported loss of superdisintegrant during coprocessing on a lab-scale spray dryer: compared to its initial content in the feed suspension, 20% to 77% w/w disintegrant was lost due to deposition of insufficiently dried particles on the inner surface of the spray dryer. In contrast, the larger dimensions of the production-scale spray dryer allowed sufficient drying and the crospovidone concentration in the spray dried particles averaged $6.12 \pm 0.04\%$ w/w and $6.07 \pm 0.07\%$ w/w for acetaminophen and ibuprofen formulations, respectively (theoretical disintegrant concentration: 6.0% w/w). Dissolution profiles of the optimised cimetidine formulation produced on a lab-scale spray dryer showed a complete release within 15 min.

4. Conclusions

A combination of mannitol, erythritol, Glucidex® 9, Kollidon® CL, colloidal silicon dioxide and polyoxyethylene 20 sorbitan monooleate was successful in improving the compactability of drug substances such as acetaminophen, ibuprofen and cimetidine via continuous co-spray drying. A highly dosed cimetidine formulation (drug concentration: 70% w/w) was produced on lab-scale equipment, while powder mixtures composed of acetaminophen (drug concentration: 70% w/w) and ibuprofen (drug concentration: 75% w/w) were successfully manufactured on a production-scale spray dryer. Direct compression of these 'ready-to-compress' powder mixtures containing acetaminophen and ibuprofen was performed without granulation, milling and/or blending steps in between spray drying and

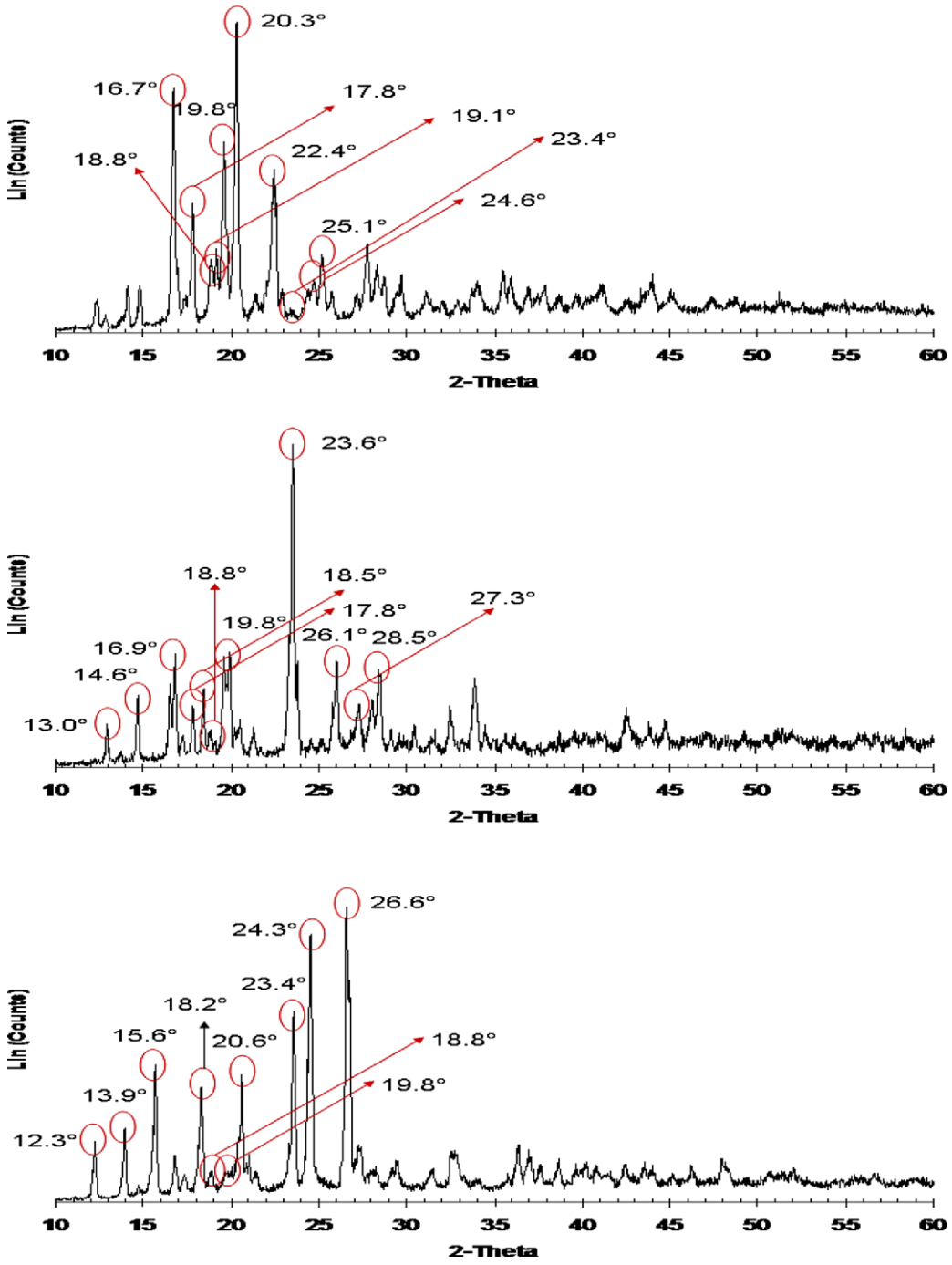

Fig. 10. X-ray diffraction pattern of optimal acetaminophen (top), ibuprofen (middle) and cimetidine (bottom) formulations.

compaction, resulting in a fully continuous manufacturing process.

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