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

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OBJECTIVES

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Tablets are still the most commonly used dosage form because of the ease of manufacturing, convenience in administration, accurate dosing and excellent stability. 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 (API) can be processed into tablets via direct compression since the majority of API lack the flow, cohesion or lubricating properties required for direct compression. Therefore, the formulator has to resort to (wet) granulation techniques to obtain API/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.

In this study an alternative method to improve the compactability of API will be developed through coprocessing of API and excipients via spray drying in order to obtain a fully continuous manufacturing process without granulation, milling and/or blending steps in between spray drying and compaction. 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. However, this concept has not been extended to the coprocessing of drug and excipient(s) to alter the physical properties of the drug. Co-spray drying is applied to generate a unique particle size, particle shape and physic-ochemical properties of the spray dried mixtures. 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. These features of coprocessing via spray drying offer many obvious economic benefits for a pharmaceutical production facility.

INTRODUCTION

SPRAY DRYING IN PHARMACEUTICAL INDUSTRY: A LITERATURE REVIEW

Abstract

Spray drying is an interesting manufacturing technique for the pharmaceutical industry since it uses a one-step process for formation and drying of powders. 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.

Spray drying has a wide range of applications in the pharmaceutical and biotech industry. It is a convenient method to produce (coprocessed) excipients. Spray drying is applied to improve the compactability of drugs and to perform microencapsulation, granulation and complex formation. In addition, spray drying is successfully used for the modification of biopharmaceutical properties and the formulation of dry powder aerosols and heat sensitive materials.

Keywords: Spray drying; Directly compressible powders; Encapsulation; Improved bioavailability; Dry powder aerosol; Heat sensitive materials

INTRODUCTION

SPRAY DRYING IN PHARMACEUTICAL INDUSTRY: A LITERATURE REVIEW

1 Introduction

Spray drying is a very widely applied technique used to dry aqueous or organic solutions, suspensions and emulsions in the food, chemical, electronics, pharmaceutical and biopharmaceutical industry. Within the food industry spray drying is used to prepare a wide range of products, e.g. baby and infant food, instant coffee, dried milk products, tomato paste. The chemical industry applies spray drying to manufacture aluminium chlorohydrate, ammonium nitrate, ammonium phosphate, magnesium hydroxide, zinc oxide, zinc sulphate, bleach powders, carbides (titanium, silicon, tantalum, niobium), catalysts for inorganic and organic chemical reactions, ceramic metals, detergents, dyestuffs, pigments, … . Electrical insulating material consists of spray dried aluminium oxide. Within pharmaceutical and biopharmaceutical industry spray drying is often selected to transform the active pharmaceutical ingredients in a powder and to manufacture solid dosage forms containing peptides, proteins or poorly water soluble active pharmaceutical ingredients. For example, antibiotics such as ampicillin, auremycin, penicillin, streptomycin, terramycin and tetracycline are spray dried, despite some activity loss (2–10%) during processing [1].

2 Spray drying process

Spray drying involves the spraying of a liquid feed formulation (solutions, suspensions, emulsions) into a hot drying medium (air, nitrogen). The droplets formed by the atomisation process are dried through solvent evaporation to form particles which are collected as a dry powder (Fig. 1) [1]. The drying of the spray continues until the desired moisture content in the dried particles is achieved, and the product is recovered from the air. It is a unique drying process since it involves both particle formation and drying. Process parameters such as inlet and outlet temperature of the drying medium and the atomisation pressure influence the physico-chemical properties of the produced powders. The characteristics of the spray dried

powder can be controlled, and the powder properties can be maintained constant throughout the continuous operation. With the different designs of spray dryers available, it is possible to select a dryer layout to produce either fine or coarse particle powders, agglomerates or granulates [1].

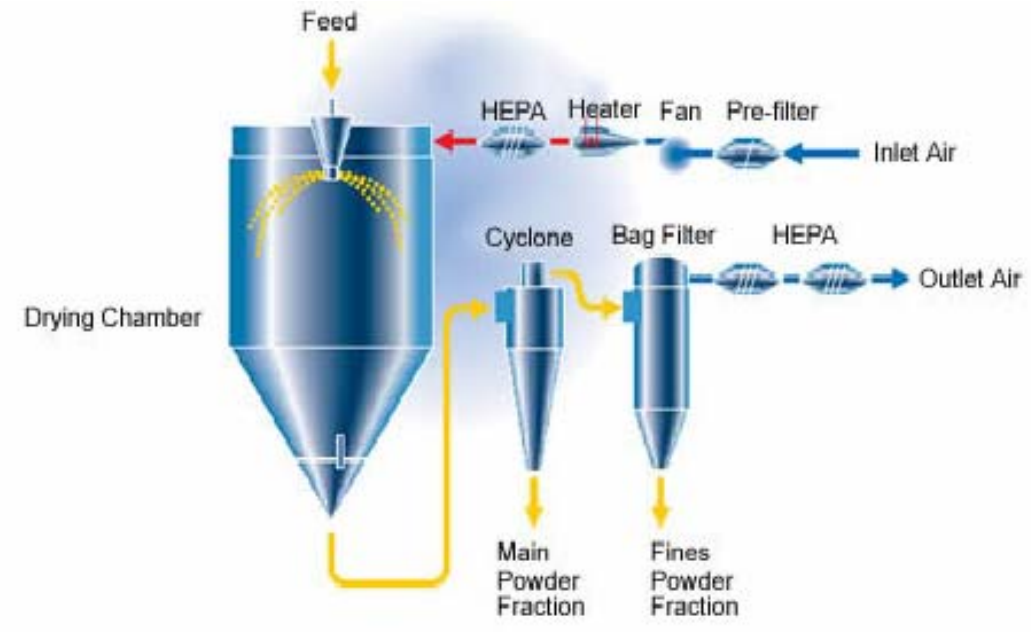

Fig. 1. Schematic overview of a spray dryer (www.niro.com)

The manner is which the spray contacts the drying air is an important factor in spray dryer design, as this had great bearing on dried product properties by influencing droplet behaviour during spray drying [1]. The different spray drying systems are open cycle, closed cycle and semi-closed cycle (Fig. 2). Open cycle systems are applied to spray dry aqueous feeds. The majority of the industrial spray dryers handle aqueous feeds and use this system. Air for drying is drawn from atmosphere and the exhaust drying air is discharged to atmosphere [2]. Before discharge the exhaust air is cleaned using combinations of cyclones, bag filters, electrostatic precipitators and scrubbers. Direct and indirect heating are applicable. Closed cycle spray dryers are used to handle flammable solvents, highly toxic products and oxygen sensitive products to avoid atmospheric pollution and/or to establish complete recovery of the evaporated solvent. The closed cycle system is based upon recycling and reusing the gaseous drying medium, which usually is an inert gas such as nitrogen. Drying chambers are incorporated with a cyclone/bag filter, solvent vapour condenser, exhaust drying medium particulate cleaning in wet scrubbers and indirect drying medium heating [2]. Semi-closed

cycle systems are classified into either the partial recycle mode (recycling of up to 60% of the exhaust air as inlet air to the dryer, for effective heat utilization) or the self-inertising mode.

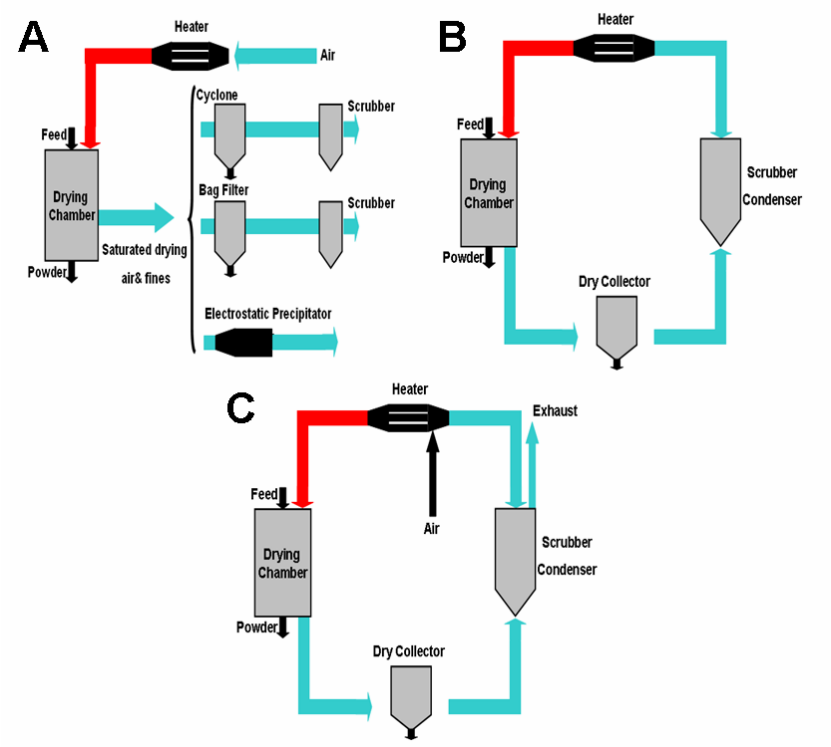

Fig. 2. Schematic outline of spray drying systems: open cycle (A), closed cycle (B) and semi-closed cycle (C) (www.niroinc.com)

Spray drying consists of 4 process stages. In the first stage the liquid feed is atomised into a spray of droplets. The atomisation stage must create a spray that when in contact with the drying medium creates optimal conditions for evaporation leading to a dry wall operation and discharging a dried product of the required properties from the drying chamber and associated dry particulate collectors [1]. The are 3 basic designs of atomisers, defined by the source of energy utilised in the droplet formation process: centrifugal energy in rotating wheel or disc atomisers, kinetic energy in pneumatic nozzle atomisers and pressure energy in pressure nozzle atomisers. Atomisers are selected according the droplet sizes to be produced in order to meet the powder specifications (Table 1) [2].

Table 1 – Median droplet size of different atomisation devices [2]

Atomisation device	Median Droplet Size (μm)
Rotary atomiser (wheel)	10 – 200
Pneumatic nozzle (two/three-fluid)	5 – 100
Pressure nozzle	30 – 350

Rotary atomisers (Fig. 3C) consist of a rotating wheel or disc. The liquid feed is introduced centrally. Rotary atomizers are reliable, easy to operate and can handle fluctuating feed rates. Further advantages include their ability to handle high feed rates and abrasive feeds [1].

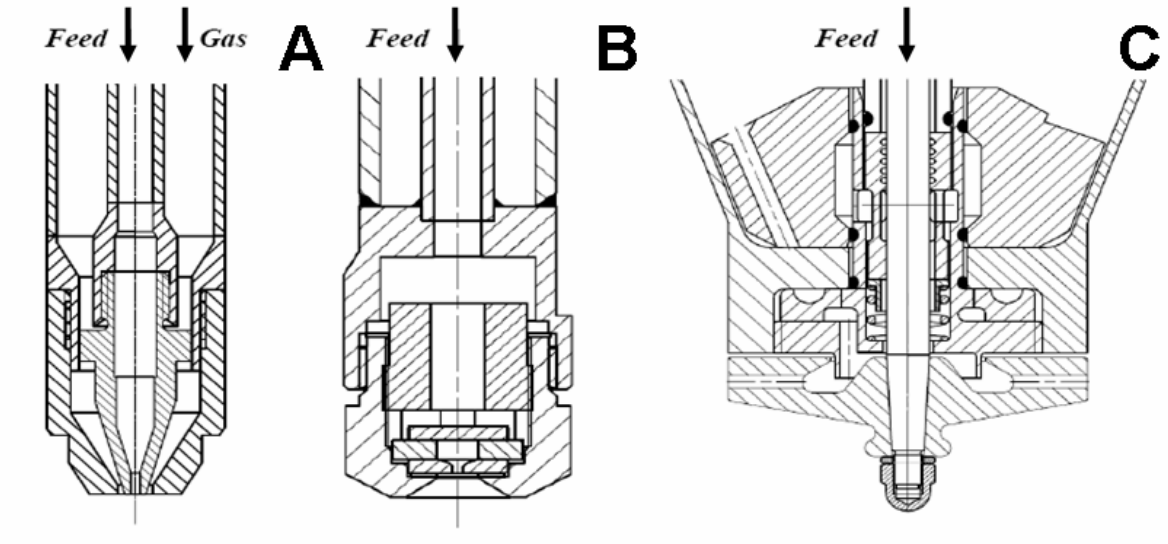

Fig. 3. Schematic outline of atomisation devices: two-fluid nozzle (A), pressure nozzle (B) and rotary atomiser (C) (www.niro.com)

Pneumatic nozzle atomisation (Fig. 3A) uses compressed air to creating high frictional forces over liquid surfaces causing liquid disintegration into spray droplets, while pressure nozzle atomisation (Fig. 3B) applies liquid feed under pressure. The feed is forced to rotate within the nozzle, resulting in cone-shaped spray patterns emerging from the nozzle orifice. Sprays from pressure nozzles are generally less homogeneous and coarser than sprays from wheels [1].

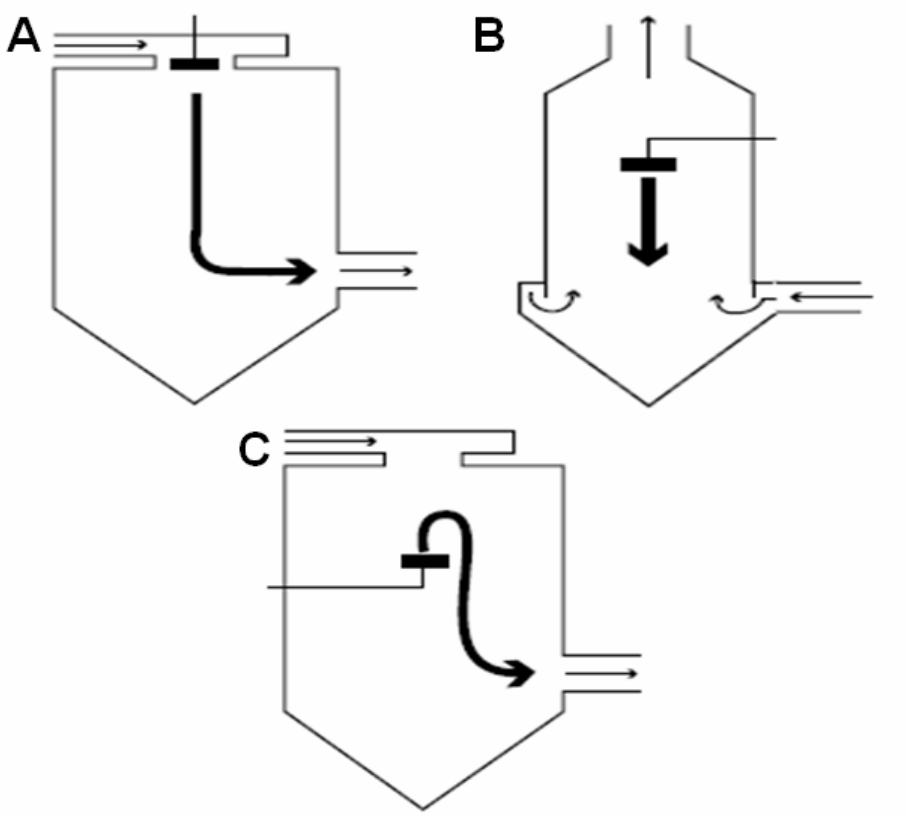

Fig. 4. Schematic outline of spray-air contact modes: co-current (A), counter-current (B) and mixed flow (C) chamber (www.buchi.com)

The second stage involves the spray-air contact, mixing and droplet/particle flow. In a co-current flow (Fig. 4A), the feed is atomised and sprayed through the drying chamber in the same direction as the flow of the heated drying medium. The droplets come into contact with the heated drying medium resulting in an optimal solvent evaporation for spray drying of heat-sensitive materials such as enzymes, peptides and proteins. In a counter-current flow design (Fig. 4B), the atomised feed and heated drying medium move in the opposite direction through the drying chamber. A counter-current flow design combines a heat treatment and also a particle agglomeration effect, resulting in increased powder flowability and median particle size for non-heat-sensitive products [1]. Spray dryer designs that combine co-current and counter-current flow modes are classified as mixed flow spray dryers (Fig. 4C). The typical fountain-type system yields coarse free-flowing spray dried powders that can be produced in drying chambers of relatively small dimensions, but the powders are subjected to higher particle temperature because partially dried particles enter the hottest region of the drying chamber near the drying medium dispenser.

The third stage combines drying and particle formation. Evaporation of the solvent takes place immediately after contact between spray droplets and the drying air. Diffusion of solvent from within the droplet maintains saturated surface conditions, resulting in a constant drying rate. When the solvent content becomes too low to maintain a saturated surface, a dry layer starts to form at the droplet surface. The atomisation of a concentrated feed suspension decreases the drying load since less water in a droplet needs to be evaporated. In addition, it is easier to achieve moisture removal from suspension-type droplets than solution-type droplets especially when the latter involves diffusion-limited film-forming characteristics at the surface [1].
Finally, particle separation from the drying air and dried product discharge takes place in the drying chamber and associated particle collection systems (cyclone, filter bag, scrubber).

3 Applications in pharmaceutical technology and drug delivery

3.1 Directly compressible powder

3.1.1 Excipient and coprocessed excipient production

Spray drying can be used to modify the size distribution, crystal habit, crystallinity content, polymorphism and moisture content if particles resulting in improved compactability.
Spray dried lactose is by far the most commonly encountered spray dried pharmaceutical excipient and is produced by spray drying a slurry containing lactose crystals. The spray dried product contains a mixture of crystals of α-lactose monohydrate and spherical agglomerates of small crystals held together by amorphous lactose [3]. Spray dried lactose was found to have significantly improved compaction properties compared to its crystalline forms. De Boer et al. [4] stated that amorphous lactose consolidated rather by plastic deformation than by particle fragmentation.
However, as specific material properties are required to allow direct compression, materials have been coprocessed via spray drying to obtain compounds having superior properties (flowability, hygroscopicity and compactability) for direct compression compared to the individual excipients or their physical mixtures [5]. During coprocessing no chemical changes

occur and all the reflected changes show up in the physical properties of the particles [3]. Several co-spray dried excipients for direct compression are commercially available: Starlac® (α-lactose monohydrate and maize starch), Cellactose® (α-lactose monohydrate and powdered cellulose), Microcelac® (α-lactose monohydrate and microcrystalline cellulose), Prosolv® (microcrystalline cellulose and silicon dioxide) and F-Melt® (mannitol, xylitol, inorganic excipient and disintegrating agent, developed for fast dissolving dosage forms) [6].

Cellactose®, a coprocessed spray dried filler/binder for direct compression and composed of 25% w/w powdered cellulose and 75% w/w α-lactose monohydrate, had a higher tablet tensile strength compared to physical powder mixtures containing 25% w/w Elcema P-100 and 75% w/w lactose for direct compression (Tablettose®) [7].

Gohel and Jogani [5] developed a multifunctional coprocessed directly compressible excipient containing lactose, polyvinylpyrrolidone and croscarmellose sodium. This product had a better flowability, compactability and tablet disintegration than α-lactose monohydrate. Hauschild and Picker [8] evaluated a coprocessed compound based on α-lactose monohydrate and maize starch for tablet formulation. Compared to its physical mixture the coprocessed material had a better flowability, a higher tablet crushing force and a faster tablet disintegration. Heckel analysis showed that the spray dried mixture deformed plastically with limited elasticity, whereas the physical mixture exhibited a predominantly elastic behaviour.

Microcelac® 100, a coprocessed spray dried filler/binder for direct compression and composed of 25% w/w microcrystalline cellulose and 75% w/w α-lactose monohydrate, showed superior flow and binding properties compared to physical mixtures of microcrystalline cellulose with different lactoses grades e.g. α-lactose monohydrate (lactose 100M), anhydric β-lactose (Pharmatose® DCL21) and spray dried lactose (Pharmatose® DCL11)[9].

3.1.2 Improved drug compressibility

Acetazolamide, an inhibitor of carbonic anhydrase, is a poorly compressible drug and usually produced through a wet granulation process. It is soluble in boiling water and in an alkaline solution. Di Martino et al. [10] compared the compressibility of acetazolamide crystals obtained by three different crystallisation processes. Firstly acetazolamide crystals were dissolved in a diluted ammonia solution and recrystallized by neutralisation with a hydrochloridric solution. Crystals of polymorphic form II were obtained. Secondly

acetazolamide crystals were dissolved in boiling demineralised water and afterwards cooled down slowly to room temperature. Only crystals of polymorphic form I were detected. Finally an ammonia solution of acetazolamide was spray dried and by this method a mixture of polymorphic form I and II was obtained. The spray dried crystals were characterised by an excellent compressibility and the absence of capping tendency while the pure polymorphic forms I and II could not be compressed into tablets [10].

3.2 Encapsulation

A microcapsule can be either an individually coated solid particle or liquid droplet, or a matrix containing many small, fine core particles. Matrix microcapsules containing drug substance and a biodegradable polymer are usually prepared by spray drying in order to obtain controlled drug release formulations [11].

Palmieri et al. [12] coprocessed ketoprofen and common pH dependent polymers (Eudragit® S and L, cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP)) via spray drying in order to prepare ketoprofen gastro-resistant microspheres. Acrylic polymers (Eudragit® S and L) showed a compactability comparable with ketoprofen/Avicel® PH 101 mixtures in contrast with the poor compactability of binary spray dried microspheres containing CAP, CAT and HPMCP. Gastro-resistance was obtained for all microspheres, although changes in drug release at low pH values were observed. Drug release was lower for microspheres containing acrylic polymers in comparison with the enteric cellulose derivates.

Binary microspheres (drug/polymer ratio: 1/2, 1/1, 2/1, 3/1, 4/1, 6/1, 9/1, 19/1) containing acetaminophen and a polymer (Eudragit® RS and RL, ethylcellulose) were manufactured via co-spray drying to prepare controlled-release solid dosage forms [13]. The compaction properties gradually improved when decreasing the acetaminophen concentration, independent of the type of polymer present in the microspheres. Although the dissolution behaviour of the microspheres was similar to that of the pure drug, tablets containing drug substance and polymer (Eudragit® RS and RL, ethylcellulose) showed controlled drug release. Eudragit® RL was less effective in slowing down the acetaminophen release because of its permeable and swellable properties.

Burke et al. [14] compared spray drying and spray-freeze drying to encapsulate darbepoetin alfa in poly(lactide-co-glycolide). In vitro and in vivo drug release was evaluated for all

microsphere formulations. Formulations prepared via spray drying and spray-freeze drying showed similar in vitro drug release, while in vivo studies detected darbepoetin alfa in serum during 4 weeks.

Feed solutions of ketoprofen/polymer (cellulose acetate butyrate (CAB), hydroxypropyl-methylcellulose phthalate (HPMCP)) mixtures in different weight ratios were spray dried in order to study the in vitro release behaviour [15]. The microparticles were formulated in hard gelatine capsule shells or compacted into tablets with the addition of maltose or hydroxypropylmethylcellulose (HPMC). All microsphere-filled capsules resulted in a rapid drug release although the microparticles with the highest concentration of CAB had the lowest release rate. In addition, tablets containing HPMC showed an initial quick release of ketoprofen during the first hour followed by a prolonged release.

3.3 Increased bioavailability

Spray drying can be used to enhance the solubility and dissolution rate of poorly soluble drugs. This usually occurs via the formation of pharmaceutical complexes or via the development of solid dispersions [11].

3.3.1 Complex formation

Cyclodextrins can be used to increase the solubility and bioavailability of poorly water soluble drug substances. Physical mixtures (1/1) containing carbamazepine and β-cyclodextrin were compared with identical solid complexes prepared via spray drying and freeze drying. These binary mixtures were blended with hydroxypropylmethylcellulose prior to compression [16]. Evaluation was based on solubility studies and in vitro release profiles. The water solubility of carbamazepine increased with increasing β-cyclodextrin content. A stronger interaction between drug substance and β-cyclodextrin was obtained in the solid complexes rather than in a simple physical mixture. In addition, binary complexes prepared via spray drying and freeze drying showed faster drug release in comparison with the physical mixtures because of an improvement in drug solubility.

Suihko et al. [17] studied the physico-chemical properties of physical mixtures, and spray dried and freeze dried solid complexes of tolbutamide and hydroxypropyl-β-cyclodextrin.

Pure hydroxypropyl-β-cyclodextrin and its tolbutamide complex were amorphous, whereas spray dried and freeze dried tolbutamide were polymorphic forms I and II, respectively.

3.3.2 Formation of solid dispersions

Valdecoxib is a selective cyclooxygenase-2 inhibitor, administered orally as an analgesic and anti-inflammatory drug. It is relatively insoluble in water. Ambike et al. [18] developed solid dispersions of valdecoxib and a hydrophilic polymer by co-spray drying. The selected hydrophilic carriers were polyvinylpyrrolidone K30 (PVP) and hydroxypropylcellulose (HPC). The saturation solubility, dissolution rate and stability of the spray dried drug, the solid dispersions and their corresponding physical mixtures were compared with the pure drug substance. All spray dried samples as well as the physical mixtures suggested increased saturation solubility and dissolution rate immediately after processing. Additionally DSC and XRPD experiments of the spray dried valdecoxib and the solid dispersions showed the generation of an amorphous form of the drug. During stability testing, the saturation solubility and dissolution rate of the solid dispersions decreased gradually over a testing period of three months. Drug crystallinity was discovered after 1 month and 15 days for respectively the drug/PVP and drug/HPC solid dispersion. The pure spray dried valdecoxib was characterized by a drastical drop in saturation solubility within 15 days.

Takeuchi et al. [19] obtained solid dispersions of indomethacin with non-porous (Aerosil® 200) and porous silica (Sylysia® 350) by spray drying an ethanol solution of indomethacin and suspended silica particles. The solid dispersions were compared with pure spray dried indomethacin concerning dissolution rate and stability. The crystallinity of spray dried indomethacin was lower, probably because of the rapid drying rate from the ethanol solution. Spray drying an ethanol solution of indomethacin in combination with silica obtained the drug in an amorphous state irrespective of the type of silica formulated. Additionally the dissolution properties of indomethacin were improved with both types of silica. Both solid dispersions and the pure spray dried indomethacin were stored for 2 months at 40°C and 75% RH. The solid dispersions with silica did not crystallise, whereas the pure spray dried form did.

Curcumin, a naturally occurring highly lipophilic molecule, has a very low aqueous solubility. Paradkar et al. [20] used spray drying to produce solid dispersions of curcumin in different ratios with polyvinylpyrrolidone (PVP). They compared the solid dispersions with their corresponding physical mixtures. Dissolution properties of the spray dried powders improved

due to the formation of an amorphous drug. Physical mixtures of curcumin and PVP showed negligible release even after 90 min, while the spray dried particles were characterised by a complete release within 30 min.

Palmieri et al. [21] carried out in vivo and in vitro studies with solid dispersions of lonidamine in polyethylene glycol 4000 (PEG) and polyvinylpyrrolidone K29/32 (PVP) for several drug/polymer ratios ranging from 1/9 to 9/1. They evaluated the dissolution rate and water solubility improvement of the drug/PEG and drug/PVP solid dispersions and compared their results with the corresponding physical mixtures. The water solubility of lonidamine was increased by the solid dispersion formation, the highest increase in solubility corresponded to the highest polymer content. During in vivo testing, they recorded an increase in bioavailability after administration of lonidamine solid dispersions in PEG and PVP.

3.4 Dry powder aerosols & heat sensitive materials

Spray drying is an excellent method for the production of dry powder formulations since particle size distribution and residual moisture content of the spray dried powders can be easily controlled by the process conditions. In addition, the processing of heat sensitive materials is feasible because the cooling effect caused by the solvent evaporation. Hence, the actual temperature of the dried product is far below the outlet temperature of the drying air.

Bosquillon et al. [22] developed an aerosol formulation for the systemic delivery of human growth hormone in rats. Spray drying a mixture of human growth hormone, lactose and dipalmitoylphosphatidylcholine yielded dry powders for pulmonary administration. Dry powder inhalation resulted in high absorption of human growth hormone, the absolute bioavailability reached 23% and the bioavailability relative to a subcutaneous injection was 56%. In contrast intratracheal instillation of a human growth hormone solution had a threefold lower systemic absorption.

Coprocessing via spray drying of bovine serum albumin (BSA) and maltodextrin (ratio: 1/1) was applied to produce dry powder aerosols for inhalation of proteins after blending with α-lactose monohydrate, modified lactoses (containing between 2.5 and 10% w/w fine particle lactose) or micronised polyethylene glycol 6000 [23].

Adler and Lee [24] investigated process stability, storage stability and surface activity of lactate dehydrogenase in co-spray dried powders. Trehalose was used as stabilising carrier. At higher inlet drying air temperature, the resulting lower residual moisture content of the

spray dried powder provided excellent storage properties, although more protein inactivation occurred. The addition of stabilising carriers (e.g. carbohydrates, amino acids) reduced the protein inactivation during spray drying. In addition, Coppi et al. [25] developed an oral formulation for lactate dehydrogenase using alginate microparticles were as a carrier to protect lactate dehydrogenase against inactivation in the gastro-intestinal tract and to improve enzyme absorption. In addition, stabilising agents (carboxymethylcellulose sodium, polyacrylic acid sodium, lactose) were added to overcome the enzymatic activity loss during spray drying.

Broadhead et al. [26] evaluated the spray drying of β-galactosidase and the influence of process and formulations parameters. Process yield was maximised at high outlet drying air temperature, although a strong decrease in enzymatic activity was measured. In addition, different stabilisers (mannitol, sucrose, arginine hydrochloride, trehalose) were tested to improve enzymatic activity, identified trehalose as the most suitable.

Sucrose was selected as suitable stabilising agent during spray drying of oxyhemoglobin and trypsinogen [27, 28]. In the absence of sucrose spray drying of oxyhemoglobin approximately 50% methemoglobin was formed, which is not suitable to transport oxygen. However, the addition of sucrose (0.25 M) as a protective agent to the feed reduced the methemoglobin production to 4%.

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CHAPTER 1

DEVELOPMENT OF DIRECTLY COMPRESSIBLE POWDERS VIA CO-SPRAY DRYING

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Abstract

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

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

CHAPTER 1

DEVELOPMENT OF DIRECTLY COMPRESSIBLE POWDERS VIA CO-SPRAY DRYING

1 Introduction

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

The purpose of this research work is to improve the compactability of a poorly compressible drug substance by coprocessing with carbohydrates via spray drying.

This chapter describes the influence of different excipients on the spray drying processibility and the physico-chemical properties (hygroscopicity, flowability and compactability) of binary and ternary mixtures containing drug substance and carbohydrates.

2 Materials and methods

2.1 Materials

2.1.1 Acetaminophen

Acetaminophen (median particle size: 50 μm) was received from Mallinckrodt Chemical (Hazelwood, USA). It has an aqueous solubility of 14 g/l and a melting point of 168-172°C (Martindale, The Extra Pharmacopoeia 28th Ed.). It is a highly dosed, poorly compressible active pharmaceutical ingredient. Acetaminophen has analgesic and antipyretic properties but it has no useful anti-inflammatory properties.

2.1.2 Monosaccharide polyols

Erythritol (C*Eridex 16955), mannitol (C*Mannidex 16700) and sorbitol (C*Sorbidex 16616) were donated by Cerestar (Mechelen, Belgium). Xylitol (Xylisorb® 90) was a gift from Roquette (Lestrem, France). The molecular weight, melting point, glass transition temperature, hygroscopicity and aqueous solubility of these compounds are shown in Table 1. Polyols are found in various fruits and vegetables and exhibit an outstanding chemical and microbiological stability. They are used as sugar substitutes because of their sweetness and reduced calorie content. In addition, the majority of these polyols can be consumed by diabetics without any significant increase in body glucose, insulin or lactic acid concentration unlike the conventional saccharides such as sucrose, glucose and lactose [4]. Mono- and disaccharide polyols have noncariogenic characteristics.

Table 1 – Physico-chemical properties of monosaccharide polyols

	Erythritol	Mannitol	Sorbitol	Xylitol
Molecular weight	122	182	182	152
Melting point (°C)	121	165	97	94
Glass transition temperature (°C)	-42	-39	-5	-22
Hygroscopicity	Very low	Very low	High	Low
Aqueous solubility (% w/w)	36	18	72	66

Erythritol (Fig. 1) was the first polyol to be industrially produced by a natural fermentation process. It is a tetrahydric polyol. Erythritol crystals are non-hygroscopic, which is of interest in applications such as tablets and dry powder aerosol formulations [5].

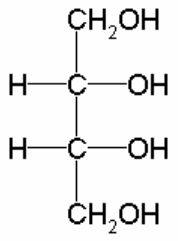

Fig. 1. Chemical structure of erythritol

Mannitol (Fig. 2) is the least soluble crystalline polyol, while sorbitol (Fig. 3) has the highest water solubility. Both are open-chain hexahydric polyols related to mannose. Because of its non-hygroscopic properties, mannitol is an excellent excipient for active pharmaceutical ingredients sensitive for moisture. They are widely used in food products and pharmaceutical formulations as diluents in direct compression [6–9] and wet granulation [10]. Spray dried and granular mannitol is used as direct compression excipient. Chewable tablets are generally containing mannitol or sorbitol [11] because of its sweet taste and cooling sensation. In addition, mannitol and sorbitol are used to process thermosensitive drugs via lyophilisation [12].

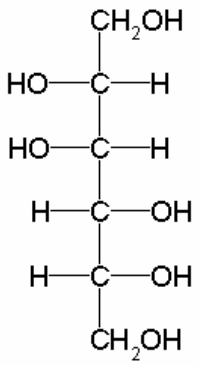

Fig. 2. Chemical structure of mannitol

Mannitol shows polymorphism (α-, β-, δ-mannitol and mannitol hemi-hydrate), while four crystalline polymorphs and one amorphous form of sorbitol have been identified [13].

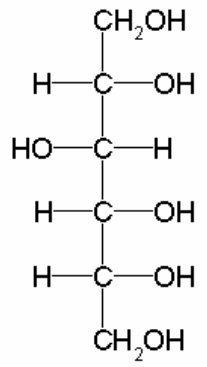

Fig. 3. Chemical structure of sorbitol

Xylitol (Fig. 4) exhibits the highest sweetness among the polyols, equal to sucrose. Therefore, it is a good candidate for chewable tablets. It is a pentahydric alcohol and is incorporated in tablets, syrups and coatings as sweetening agent [6, 8]. Xylitol is commercially available in powdered form and in several directly compressible granular forms.

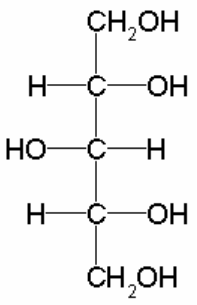

Fig. 4. Chemical structure of xylitol

2.1.3 Disaccharide polyols

Isomalt (C*Isomaltidex 16500) was donated by Cerestar (Mechelen, Belgium), while lactitol (Finlac™ DC) was supplied by Danisco (Copenhagen, Denmark). Maltitol (Maltisorb® P90) was a gift from Roquette (Lestrem, France). The molecular weight, melting point, glass transition temperature, hygroscopicity and aqueous solubility are shown in Table 2.

Table 2 – Physico-chemical properties of disaccharide polyols

	Isomalt	Lactitol	Maltitol
Molecular weight	344	344	344
Melting point (°C)	147	122	150
Glass transition temperature (°C)	34	33	47
Hygroscopicity	Low	Medium	Low
Aqueous solubility (% w/w)	28	58	60

Isomalt (Fig. 5) is mixture of hydrogenated mono- and disaccharides whose principal components are the disaccharide alcohols 1,6-glucopyranosyl-D-sorbitol (GPS) and 1,1-glucopyranosyl-D-mannitol (GPM). Isomalt is a non-cariogenic excipient used in a variety of pharmaceutical preparations including tablets, capsule coatings and suspensions. Isomalt has been used for extrusion purposes to develop a directly compressible excipient [14–15]. Isomalt crystals are non-hygroscopic, which is a significant property for their use in hard candies and coatings. Based on its glass transition temperature of 34°C, isomalt is in a glassy state at room temperature and it does not crystallise under these conditions.

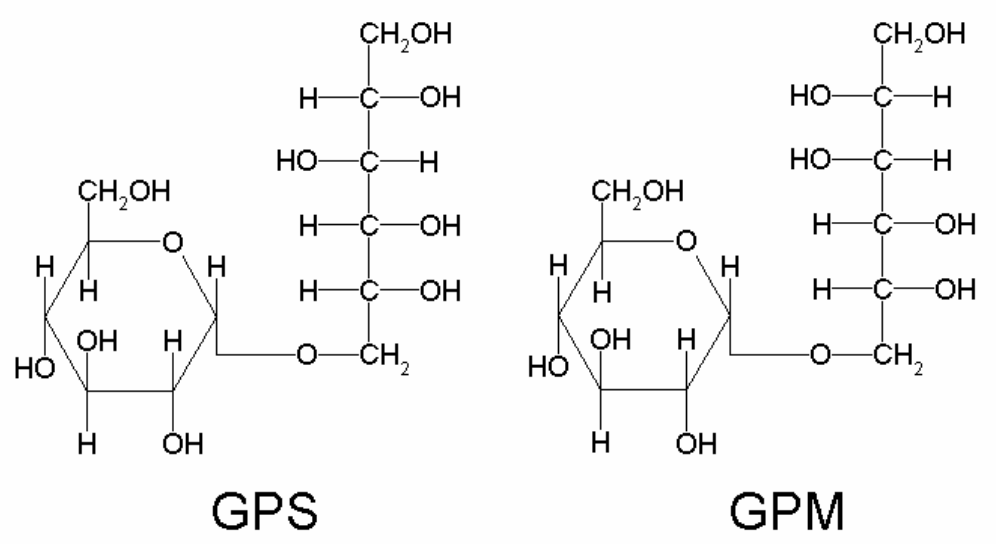

Fig. 5. Chemical structure of isomalt

Lactitol (Fig. 6) is a disaccharide with many similar characteristics to sucrose, hence it can be a direct replacement for sucrose in many applications. It occurs as orthorbombic crystals and shows polymorphism [16]. Today oral tablets and lozenges are not only produced using conventional saccharides (sucrose, glucose and lactose), but also, to increasing extent, using

sugar substitutes (mono- and disaccharide alcohols, also called polyols) like sorbitol, xylitol, lactitol or isomalt [17].

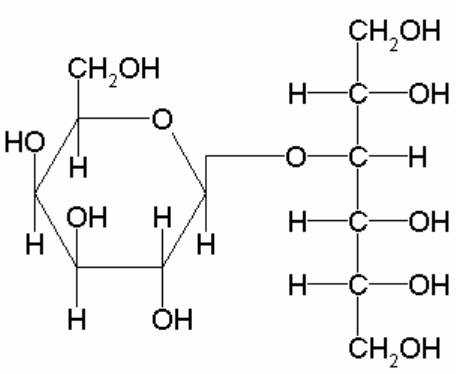

Fig. 6. Chemical structure of lactitol

Maltitol (Fig. 7) is used as a carrier in dry powder inhalers [18]. In addition, maltitol is incorporated as a diluent in different oral dosage forms prepared via wet granulation and direct compression [19].

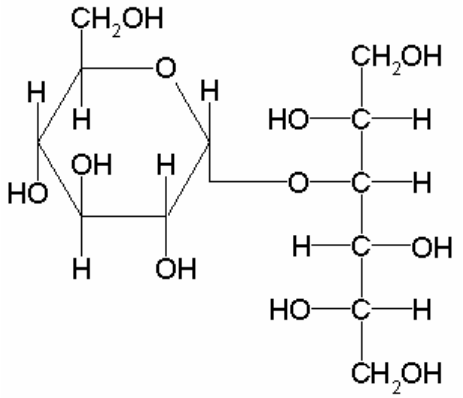

Fig. 7. Chemical structure of maltitol

2.1.4 Lactose

Lactose (Respitose® SV003) was obtained from DMV International (Veghel, The Netherlands). Several forms are commercially available: anhydrous α-lactose, α-lactose monohydrate and to a lesser extent anhydrous β-lactose. Its melting point depends on its forms (anhydrous α-lactose: 223°C, α-lactose monohydrate: 201°C, anhydrous β-lactose: 252°C). Various lactose grades (e.g. spray dried and granulated) characterised by different particle size distribution, particle shape and density are commercially available [20]. Spray

dried lactose contains approximately 85% α-lactose monohydrate and 15% amorphous lactose, resulting in improved compactability. In addition, coprocessed excipients for direct compression containing lactose are commercially available: Starlac® [21] (α-lactose monohydrate and maize starch), Cellactose® [22] and Microcelac® [23] (α-lactose monohydrate and cellulose).

Lactose (Fig. 8) is widely used as a diluent in capsules and tablets prepared via wet or dry granulation and direct compression [24–26]. In addition, applications include lactose as a carrier in dry powder formulations produced via lyophilisation and/or spray drying [27–29].

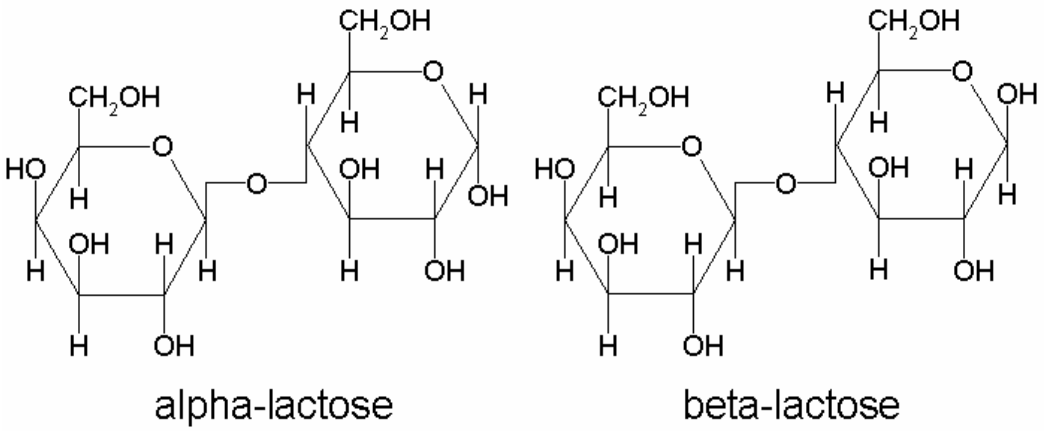

Fig. 8. Chemical structure of lactose

2.1.5 Maltodextrin

Maltodextrin (Glucidex® 2) was a gift from Roquette (Lestrem, France). Maltodextrin, a starch conversion product, is a nutritive saccharide mixture of polymers that consist of D-glucose units, with a dextrose equivalent (DE) less than 20. These units are linked primarily by (α-1,4)-bonds, but there are branched segments linked by (α-1,6)-bonds. Similar to starch, maltodextrin is composed of a mixture of amylose and amylopectin (Table 3), the ratio of both products affecting the physico-chemical properties of maltodextrins.

Table 3 – Physico-chemical properties of amylose and amylopectin

Characteristic	Amylose	Amylopectin
Shape	Essential linear	Branched
Linkage	α-1,4 (some α-1,6)	α-1,4 and α-1,6
Molecular Weight	< 0.5 million	50-500 million
Film forming	Strong	Weak
Gelling	Firm	Soft
Colour with Iodine	Blue	Reddish Brown
Starch	**Amylose (%)**	**Amylopectin (%)**
Maize (corn)	25	75
Waxy maize	1-5	95-99
Wheat	25	75
Potato	20	80
Tapioca	17	83
High Amylose Maize	50-70	30-50

Amylose (Fig. 9) is an essential linear polysaccharide of α-D-glucose. Amylopectin (Fig. 10) is a highly branched polysaccharide of α-D-glucose, differs from amylose in being highly branched and is completely insoluble in water.

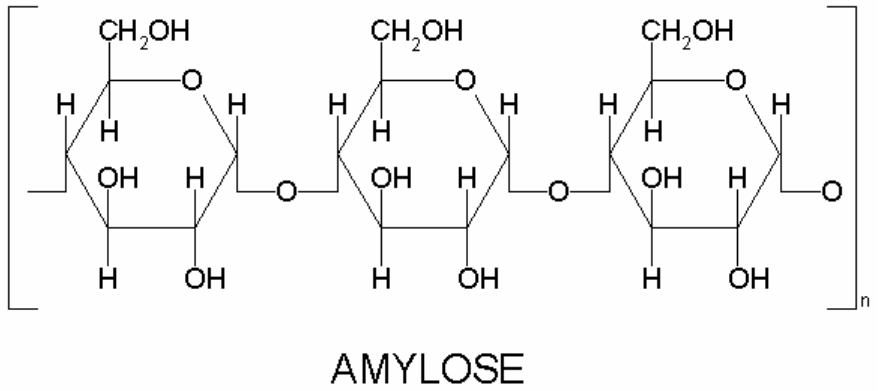

Fig. 9. Chemical structure of amylose

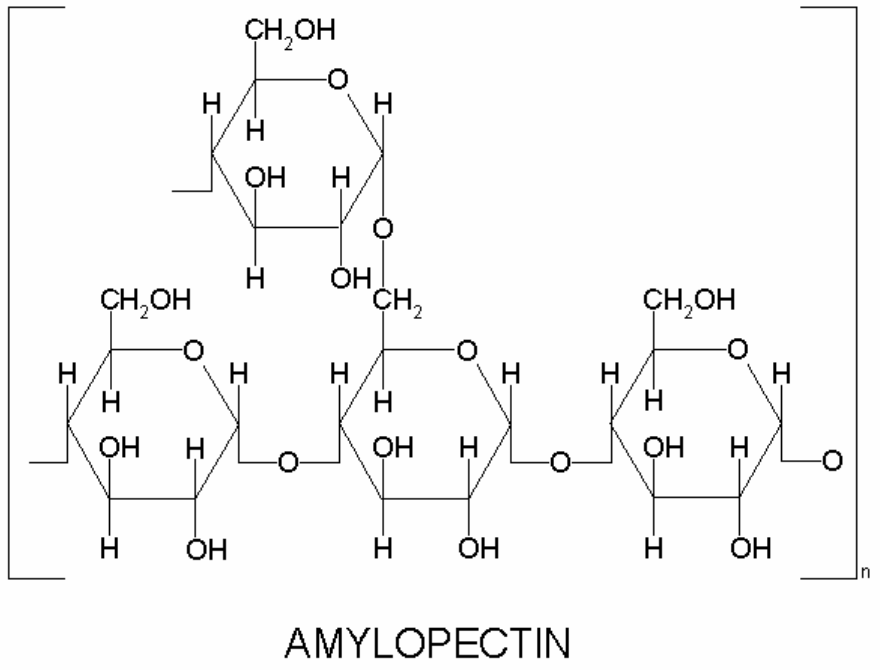

Fig. 10. Chemical structure of amylose

The properties of maltodextrin vary with its grade and DE value. Maltodextrin is a hygroscopic and freely soluble excipient. The solubility, hygroscopicity and sweetness of this excipient increase as the DE value increases, while the compressibility decreases. It is a coating agent, viscosity-enhancing agent, tablet diluent and binder used in direct compression and wet granulation [30–32].

2.1.6 Colloidal silicon dioxide

Colloidal silicon dioxide (Aerosil® 200) was purchased from Federa (Brussels, Belgium). It is applied to improve the flow properties of powders intended for tablet and capsule manufacturing.

2.1.7 Magnesium stearate

Magnesium stearate was purchased from Federa (Brussels, Belgium). It is widely used in pharmaceutical formulations, primarily as a lubricant in capsule and tablet formulations at concentrations between 0.25–5.0% w/w. Magnesium stearate is hydrophobic and may retard the drug dissolution from a solid dosage forms. The lowest possible concentration is therefore used in tablet and capsule formulations [33–35].

2.2 Methods

2.2.1 Preparation of the spray dried particles

Aqueous solutions of pure acetaminophen (total solid content: 1.2% w/w) and of acetaminophen and a carbohydrate (erythritol, isomalt, lactitol, lactose, maltitol, maltodextrin, mannitol, sorbitol and xylitol) (drug/carbohydrate ratio: 1/1, total solid content: 2.4% w/w) were prepared. Spray drying of these solutions was performed in a lab-scale Mobile Minor spray dryer (GEA NIRO, Copenhagen, Denmark). The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and 60° conical base. The solutions were fed to a two-fluid nozzle (diameter: 1 mm) at the top of the spray dryer by means of a peristaltic pump, type 520U (Watson Marlow, Cornwall, UK) and a Marprene® tube (inside diameter: 4.8 mm) (Watson Marlow, Cornwall, UK). The spray dryer operated in co-current air flow. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature, sieved (375 μm) and stored in sealed vials (room temperature, ambient relative humidity) prior to their characterisation and further use. Pure acetaminophen and drug/excipient mixtures (1/1) containing erythritol, isomalt, lactitol, lactose, maltitol, maltodextrin, mannitol, sorbitol and xylitol were prepared via spray drying using the parameters of process 1 (Table 4).

Table 4 – Process conditions during spray drying in the Mobile Minor spray dryer (GEA NIRO)

Process Parameters	Process 1	Process 2
Feed Rate (g/min)	30.5	38.5
Inlet Drying Air Temperature (°C)	140	220
Outlet Drying Air Temperature (°C)	60	80
Drying Gas Rate (kg/h)	80	80
Atomising Air Pressure (bar)	1	2
Compressed Air Flow (%)	55	50

To investigate the influence of spray drying parameters on the compaction behaviour of drug/excipient mixtures, binary solutions (1/1) containing erythritol, maltodextrin and mannitol were co-spray dried via process 2 (Table 4). These settings were selected in order to

decrease the residual moisture content of the spray dried powders using higher drying air temperatures and atomisation pressure.

In addition to the binary drug/carbohydrate powders, ternary powder mixtures were prepared via spray drying of aqueous drug/mannitol/excipient solutions and compared with drug/mannitol mixtures (1/1) produced according to process 2 (Table 4). Acetaminophen, mannitol and a water soluble carbohydrate (erythritol and maltodextrin) were dissolved in demineralised water at room temperature (drug/mannitol/excipient ratio: 1/0.7/0.3 and 1/0.9/0.1, total solid content: 2.6% w/w). These solutions were spray dried according to process 2 (Table 4).

2.2.2 Evaluation of spray dried powders

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

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

The hygroscopic behaviour of the powders was investigated by storing the spray dried powders in sealed boxes containing saturated salt solutions, which maintained a specific relative humidity depending of the salt. The salts used and the corresponding relative humidities are magnesium chloride (33.0% RH), magnesium nitrate (52.8% RH), 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 thermal behaviour of the binary spray dried mixtures was compared with their physical mixtures using differential scanning calorimetry. Modulated temperature DSC experiments (heating rate: 2°C/min, modulation amplitude: 0.5°C, modulation period: 60 s and temperature range: -40–300°C) were performed using a DSC 2920 calorimeter (TA Instrument, New Castle, USA) with a DSC refrigerated cooling system (TA Instruments, New Castle, USA).

The flowability of spray dried powders (n: 5) was measured according to the method described in the European Pharmacopoeia 5th Ed. (automated powder flowability analyser, Type PTG-2, PharmaTest, Hainburg, Germany) using a 25 mm nozzle. An electrical stirrer (speed: 25 rpm) was used to avoid bridging in the funnel for material having poor flowability.
The bulk density of the spray dried powders was determined via the method described in the European Pharmacopoeia 5th Ed. using 20 g of powder and a 100 ml graduated cylinder.
SEM images were recorded with a Quanta 200 FEG (FEI, Eindhoven, The Netherlands) scanning electron microscope operated at an acceleration voltage of 5 kV. The powder was deposited onto a carbon carrier substrate.

2.2.3 Tabletting process and evaluation

The spray dried powders were blended (TSA Turbula mixer, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 0.3% w/w colloidal silicon dioxide for 10 min in a first mixing step and with 0.5% w/w magnesium stearate for 5 min in a second mixing step. Glidant, lubricant and spray dried powders were sieved (375 μm) before blending. The powder mixtures were compacted (n: 10, 500 ± 5 mg) on an excentric tablet press, Type EKO (Korsch, Berlin, Germany) equipped with 13.0 mm circular flat punches. The tablet properties were evaluated at two different compaction pressures (74 MPa and 111 MPa).
Based on the diametral crushing strength of the tablets, determined using a hardness tester, Type PTB (Pharma Test, Hainburg, Germany), the tensile strength of the tablets was calculated according to Fell and Newton [36].

2.2.4 Heckel analysis

The porosity-compression pressure function according to Heckel was calculated. Flat-faced compacts (n: 3, 500 ± 5 mg, diameter: 13 mm) of drug/excipient mixtures produced according to process 1 and 2 were prepared on a compaction simulator (ESH, Brierley Hill, UK) at a maximum load of 110 MPa. While the lower punch was stationary during compaction, the upper punch displacements followed a sine wave. The average punch speed during compaction was 3 mm/s. Data were compensated for punch deformation during compression. Final thickness and diameter of the tablets were measured with an electronic digital calliper (Bodson, Luik, Belgium). The true density was defined using a helium gas pycnometer,

Accupyc 1330 (Micromeritics, Norcross). The following analysis parameters were used: 10 purges, 10 runs and 19.5 psig as purge and run fill pressure.
The Heckel equation (Eq. 1) [37] is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the compactability of the powder bed as the product.

$$\text{Ln}\,(1/\,(1 - D) = kP + A \qquad (1)$$

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

3 Results and discussion

Acetaminophen was used as model drug because of its poor compactability as evidenced during this study by the low tablet tensile strength (0.38 and 0.67 MPa at a compression pressure of 74 MPa and 111 MPa, respectively) as well as capping and lamination problems after compaction of pure spray dried acetaminophen. This behaviour was due to the formation of monoclinic acetaminophen crystals during spray drying, exhibiting a relatively high elastic deformation [38]. Therefore, acetaminophen was coprocessed with water soluble carbohydrates to improve tablet tensile strength and to overcome capping and lamination problems.
The screened drug/excipient mixtures (1/1) were divided in three groups according to their spray drying processibility. Spray drying of drug/excipient mixtures (1/1) containing isomalt and sorbitol was not feasible because of process problems. Coprocessing of aqueous acetaminophen/sorbitol solutions (1/1) resulted in vitrification of sorbitol forming a transparent layer on the surface of the drying chamber wall, pipings and cyclone. Powder mixtures containing isomalt completely blocked pipings and cyclone during spray drying as too much material accumulated in the pipings and cyclone. The second group consists of drug/excipient mixtures (1/1) composed of lactitol, maltitol and xylitol, which could be spray dried despite some process problems. Due to their gummy-like and thermoplastic nature, and high residual moisture content (Table 5), an important fraction of these binary powder

mixtures adhered to the drying chamber wall surfaces, pipings and/or cyclone, resulting in low process yields (lactitol: 40%, maltitol: 43%, xylitol: 61%)(Table 5).

These problems occur regularly in spray drying operations [39] and can be caused by various factors: inappropriate drying resulting in high water content and sticky character of the spray dried powder, thermoplastic and/or hygroscopic nature of the dried product under the temperature and humidity conditions within the drying chamber. The third group consists of erythritol, lactose, maltodextrin and mannitol, which yielded non-sticky powders after co-spray drying with acetaminophen. In contrast to erythritol-, maltodextrin- and mannitol-containing powders, lactose mixtures had a low yield probably caused by low drying temperatures. Normally lactose solutions or suspensions are spray dried at higher inlet and outlet drying temperatures of e.g. 170–190°C and 85–100°C, respectively [40–42]. Even for the best binary drug/excipient mixtures the process yield was below 90% (70, 82 and 75% for erythritol, maltodextrin and mannitol, respectively)(Table 5), which is economically unprofitable. However, it should be emphasised that spray drying was performed in a lab-scale drier which typically has a lower yield – in comparison to production-scale spray dryers – due to higher wall deposits, since air residence times and radial distances from the atomiser to the drying chamber wall are shorter [39].

Table 5 – Spray drying process yield and residual moisture content after spray drying

Formulation	Yield (% w/w)	Residual Moisture Content (% w/w)
Acetaminophen/Lactitol	40	2.90
Acetaminophen/Maltitol	43	7.40
Acetaminophen/Xylitol	61	4.72
Acetaminophen/Erythritol	70	0.60
Acetaminophen/Lactose	54	3.12
Acetaminophen/Maltodextrin	82	7.10
Acetaminophen/Mannitol	75	0.89

Because aqueous drug/excipient solutions (1/1) composed of isomalt, lactitol, maltitol, sorbitol and xylitol were ineffective to coprocess via spray drying, only binary mixtures containing erythritol, lactose, maltodextrin and mannitol were evaluated on powder hygroscopicity. Spray drying drug/excipient solutions (1/1) containing erythritol and mannitol

resulted in crystalline non-hygroscopic powder mixtures (Fig. 11). Modulated DSC experiments showed fractions of amorphous lactose and completely amorphous maltodextrin in their corresponding spray dried drug/excipient mixtures. However, the drug/lactose mixtures were non-hygroscopic, while the use of maltodextrin resulted in a hygroscopic powder absorbing about 8.5% water at a relative humidity above 50% (Fig. 11).

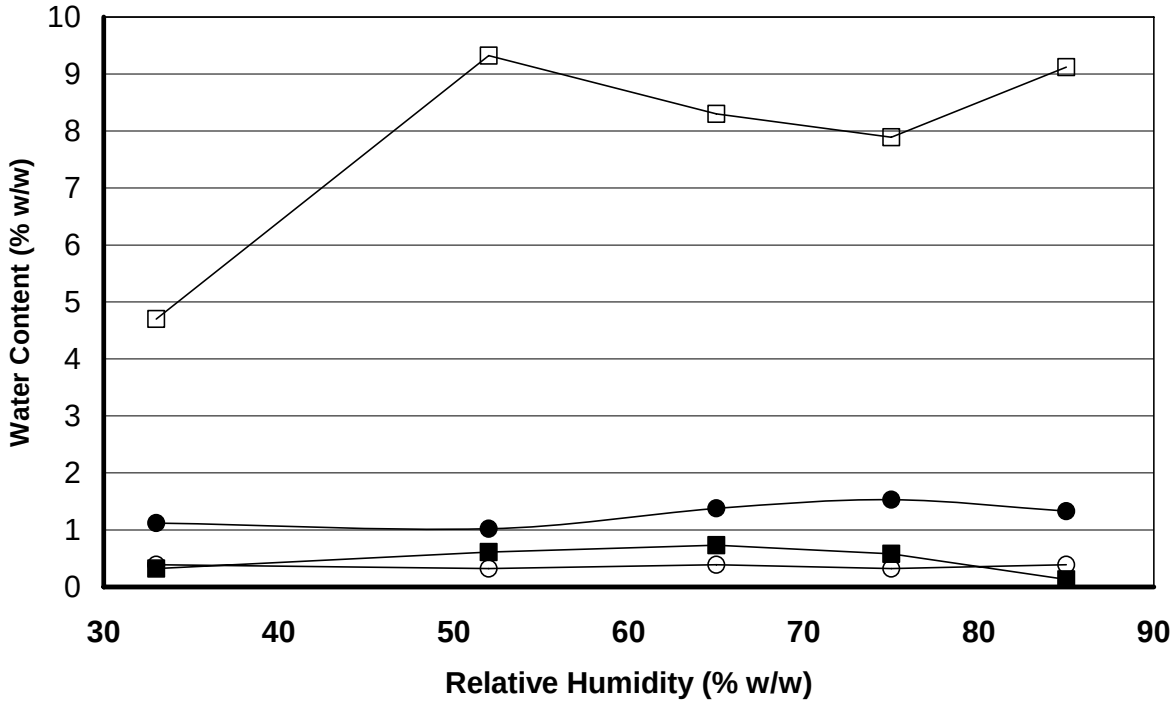

Fig. 11. Hygroscopicity of acetaminophen/excipient powder mixtures (1/1) containing erythritol (○), lactose (●), maltodextrin (□) and mannitol (■)

A good flowability of the powders is required to ensure a consistent tablet weight. Erythritol and mannitol binary mixtures were characterised by a powder flow time of 4.8 ± 0.7 and 5.9 ± 0.5 s/100g, respectively, indicating acceptable flowability. Binary mixtures (1/1) containing maltodextrin illustrated poor flowability with a powder flow time of 76.6 ± 30.4 s/100g. Powders containing lactose did not flow through the nozzle. Consequently, drug/lactose mixtures (1/1) were eliminated for further evaluation. The bulk densities of drug/excipient mixtures (1/1) containing erythritol, maltodextrin and mannitol were 0.526, 0.192 and 0.439 g/ml, respectively. SEM pictures (Fig. 12) of drug/excipient mixtures containing erythritol and mannitol showed large oblong particles and irregular agglomerates, respectively, resulting in better powder flowability in comparison with the cohesive powder mixtures containing maltodextrin and lactose which consisted of small particles.

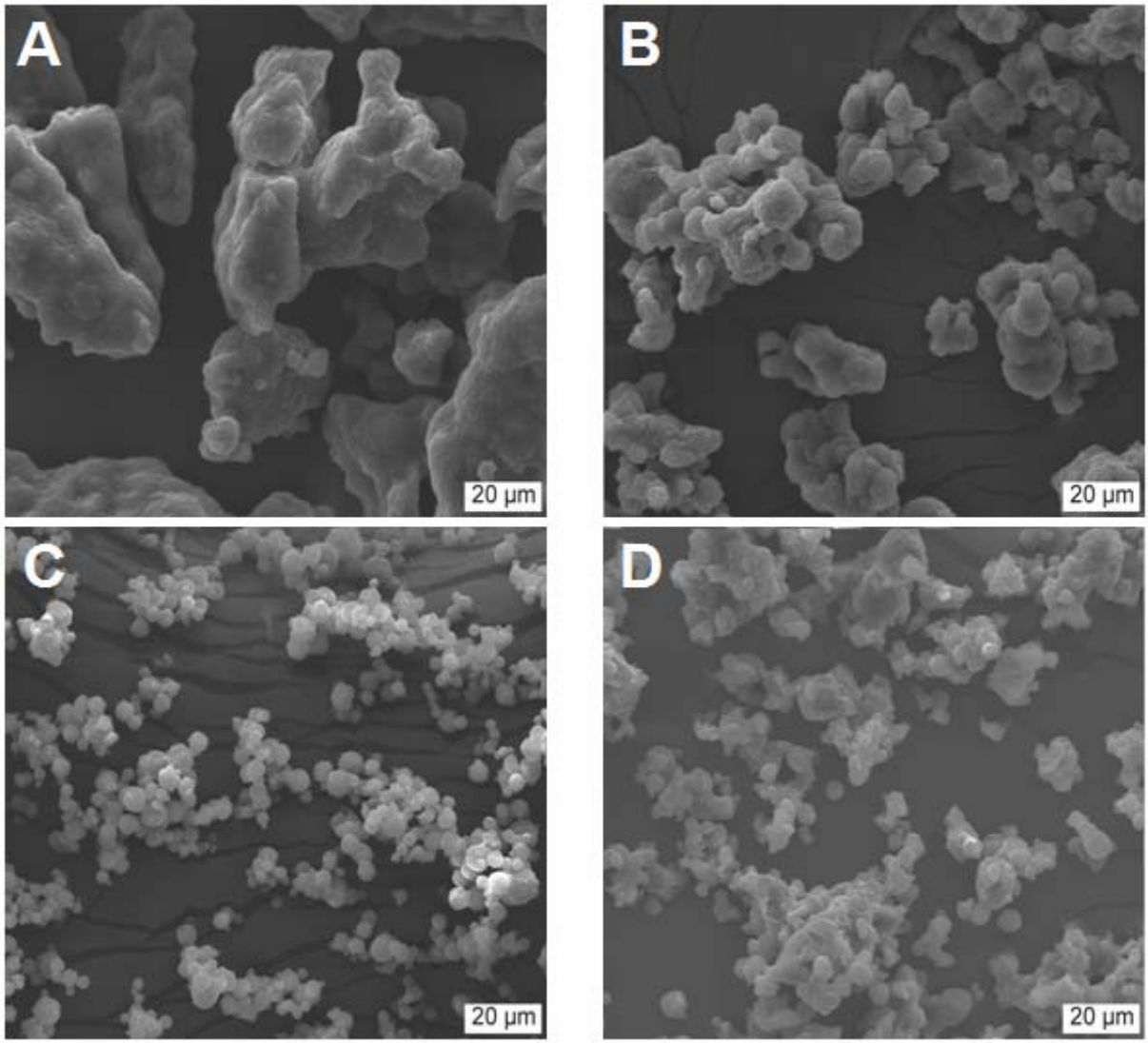

Fig. 12. SEM pictures of acetaminophen/excipient powder mixtures (1/1) containing erythritol (A), mannitol (B), maltodextrin (C) and lactose (D)

Coprocessing of acetaminophen with erythritol, maltodextrin or mannitol prevented tablet capping and lamination, despite the fact that X-ray diffraction showed that these binary mixtures contained monoclinic acetaminophen crystals. Powder X-ray data of pure monoclinic and orthorhombic acetaminophen have been proposed by Nichols and Frampton [43]. The orthorhombic acetaminophen polymorph, having better tabletting properties [44], was not formed during co-spray drying. The addition of maltodextrin and mannitol to the formulation improved tablet tensile strength in comparison with pure spray dried acetaminophen, whereas drug/erythritol mixtures provided comparable tablet tensile strength (Table 6). One-way ANOVA (SPSS 12.0) showed significant differences in tablet tensile strength between pure spray dried acetaminophen and drug/carbohydrate mixtures containing

maltodextrin and mannitol as well as between binary mixtures composed of maltodextrin and mannitol.

Process conditions during spray drying (drying temperatures and atomisation pressure) affected the tabletting properties of acetaminophen/carbohydrate mixtures: at a compaction pressure of 74 MPa the tablet tensile strength was significantly higher when both the process temperatures and the atomisation pressure were higher (Table 6). Compaction at 111 MPa showed a similar trend.

Table 6 – Influence of spray drying parameters on tablet tensile strength (n: 10, mean ± st.dev.) (compression pressure: 74 MPa)

Formulation	Tablet Tensile Strength (MPa)	
	Process 1	Process 2
Pure Spray Dried Acetaminophen	0.38 ± 0.14	/
Acetaminophen/Erythritol	0.45 ± 0.09	0.64 ± 0.16
Acetaminophen/Maltodextrin	0.88 ± 0.15	2.39 ± 0.52
Acetaminophen/Mannitol	0.72 ± 0.11	1.49 ± 0.21

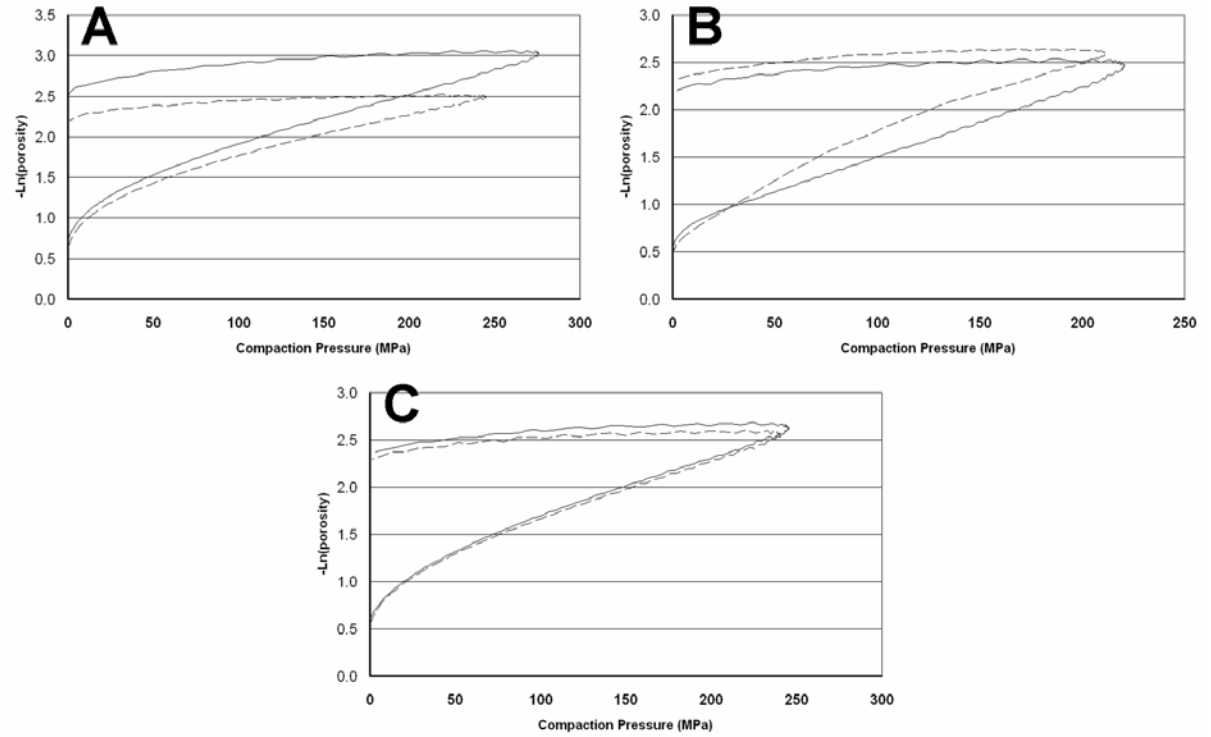

Fig. 13. Heckel plots of acetaminophen/excipient powder mixtures (1/1) containing erythritol (A), maltodextrin (B), mannitol (C) produced via process 1 (_____) and process 2 (- - - - -)

The influence of these process conditions (drying temperatures and atomisation pressure) on the powder compactability was investigated using Heckel analysis (Table 7) (Fig. 13). As most pharmaceutical materials undergo particle fragmentation during initial loading followed by elastic and/or plastic deformation at higher loads [45], the fragmentation behaviour was evaluated by linear regression (R^2) of the initial phase of the compression (2–50 MPa). A decrease of R^2 indicates an increase of particle fragmentation, resulting in increased particle bonding surfaces. The reciprocal of the slope (P_y, yield pressure) of the linear part of the compression curve (40–110 MPa) reflected the total deformation [46], a decrease in yield pressure pointing to more plastic deformation behaviour [47].

Table 7 – Heckel analysis (n: 3, mean ± st.dev.) of 2-component mixtures after co-spray drying using different process parameters

Formulation	Spray Drying Process	True Density (g/ml)	Heckel Analysis	
			R^2	P_Y (MPa)
Acetaminophen/Erythritol	Process 1	1.3723	0.9663 ±0.00156	129.1 ± 0.97
	Process 2	1.3762	0.9579 ± 0.00052	145.8 ± 2.91
Acetaminophen/Maltodextrin	Process 1	1.4507	0.9720 ± 0.00063	135.7 ± 2.79
	Process 2	1.4776	0.9958 ± 0.00070	93.6 ± 1.65
Acetaminophen/Mannitol	Process 1	1.3844	0.9785 ± 0.00058	129.9 ± 1.02
	Process 2	1.3864	0.9697 ± 0.00074	133.3 ± 0.53

P_Y: (Yield Pressure)

Heckel analysis confirmed that the improved tablet tensile strength at higher process temperatures and atomisation pressure (process 2) was caused by an increased particle fragmentation of crystalline erythritol and mannitol mixtures, while an increased plastic deformation of amorphous maltodextrin formulations provided stronger tablets. Amorphous particles were less prone to fragment but more deformable in comparison to crystalline particles [48–49].

Based on the characterisation of the spray dried binary powders and the influence of the different carbohydrates on tablet properties, erythritol, maltodextrin and mannitol were selected as excipients for the coprocessing of ternary mixtures with acetaminophen. In

addition to the active ingredient, mannitol was used as the main fraction of these ternary mixtures, based on its positive effects on powder hygroscopicity, flowability and compactability observed for the binary mixture. Erythritol or maltodextrin were added as third component to improve flowability and tablet strength, respectively, without a strong negative effect on process yield and/or powder hygroscopicity. The lower content limit of erythritol and maltodextrin (drug/mannitol/excipient ratio: 1/0.9/0.1) was chosen to realise a significant improvement of flowability and tablet tensile strength, respectively, while the maximum content of erythritol and maltodextrin (drug/mannitol/excipient ratio: 1/0.7/0.3) was limited to avoid a strong negative influence on tablet tensile strength and hygroscopicity, respectively.

Spray drying of ternary mixtures containing erythritol and maltodextrin was extremely efficient and provided similar process yields (71 to 74%) in comparison with the reference formulation containing only drug and mannitol (ratio 1/1) (73%). The hygroscopic behaviour of the ternary mixtures was also similar with drug/mannitol mixtures (1/1): all were characterised as non-hygroscopic, only the maltodextrin formulations had a slightly higher but acceptable water uptake as a function of maltodextrin content (Fig. 14).

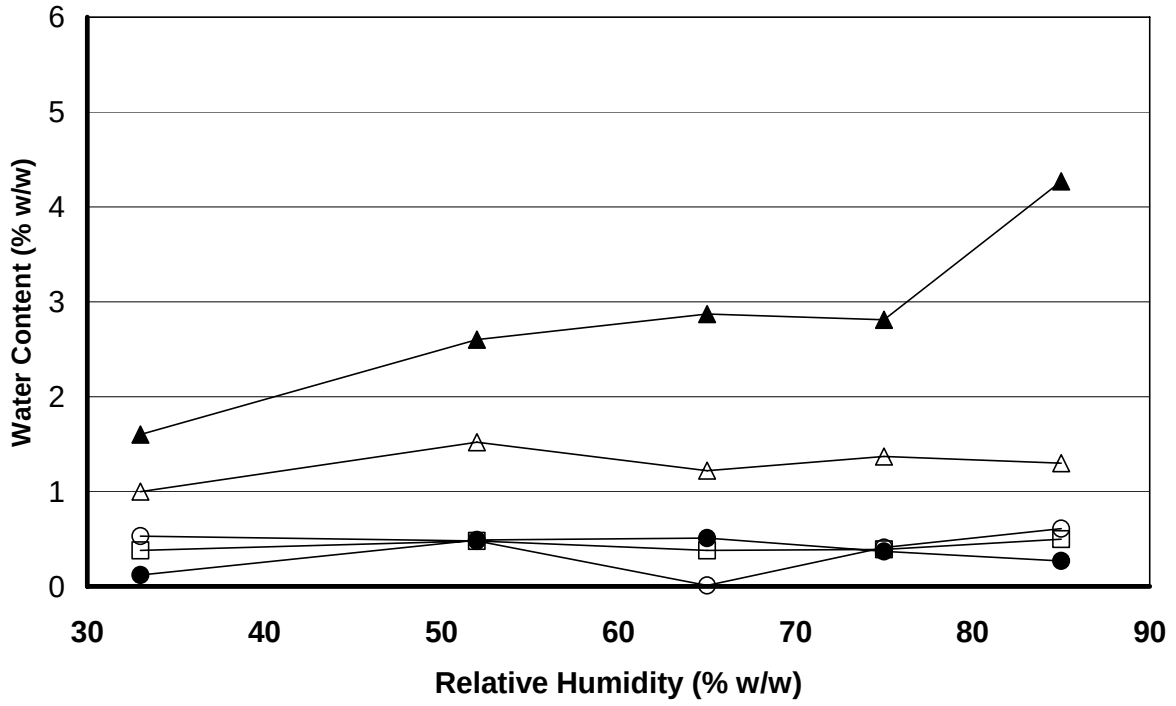

Fig. 14. Hygroscopicity of reference formulation (acetaminophen/mannitol powder mixture (1/1)) (□) and acetaminophen/mannitol/excipient powder mixtures containing erythritol (1/0.7/0.3) (●) and erythritol (1/0.9/0.1) (○), maltodextrin (1/0.7/0.3) (▲) and maltodextrin (1/0.9/0.1) (△)

Powder flowability (Fig. 15) of all spray dried ternary mixtures was improved in comparison with the binary reference formulation. Using a higher concentration of erythritol or maltodextrin (ratio 1/0.7/0.3) showed better flowability in comparison with their corresponding formulations (ratio 1/0.9/0.1) because of increased particle size (Fig. 16). Similar to the binary mixtures the best flowability was obtained for formulations containing erythritol.

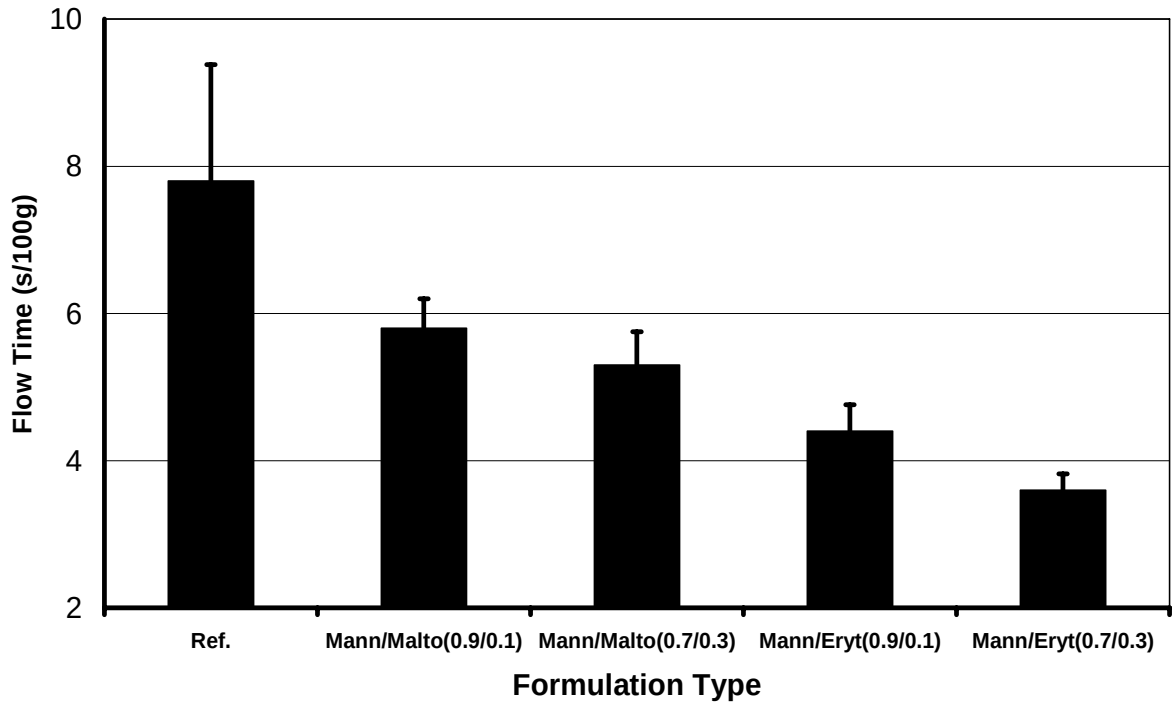

Fig. 15. Flowability of reference formulation (acetaminophen/mannitol powder mixture (1/1)) and acetaminophen/mannitol/excipient powder mixtures (1/0.7/0.3) and (1/0.9/0.1)

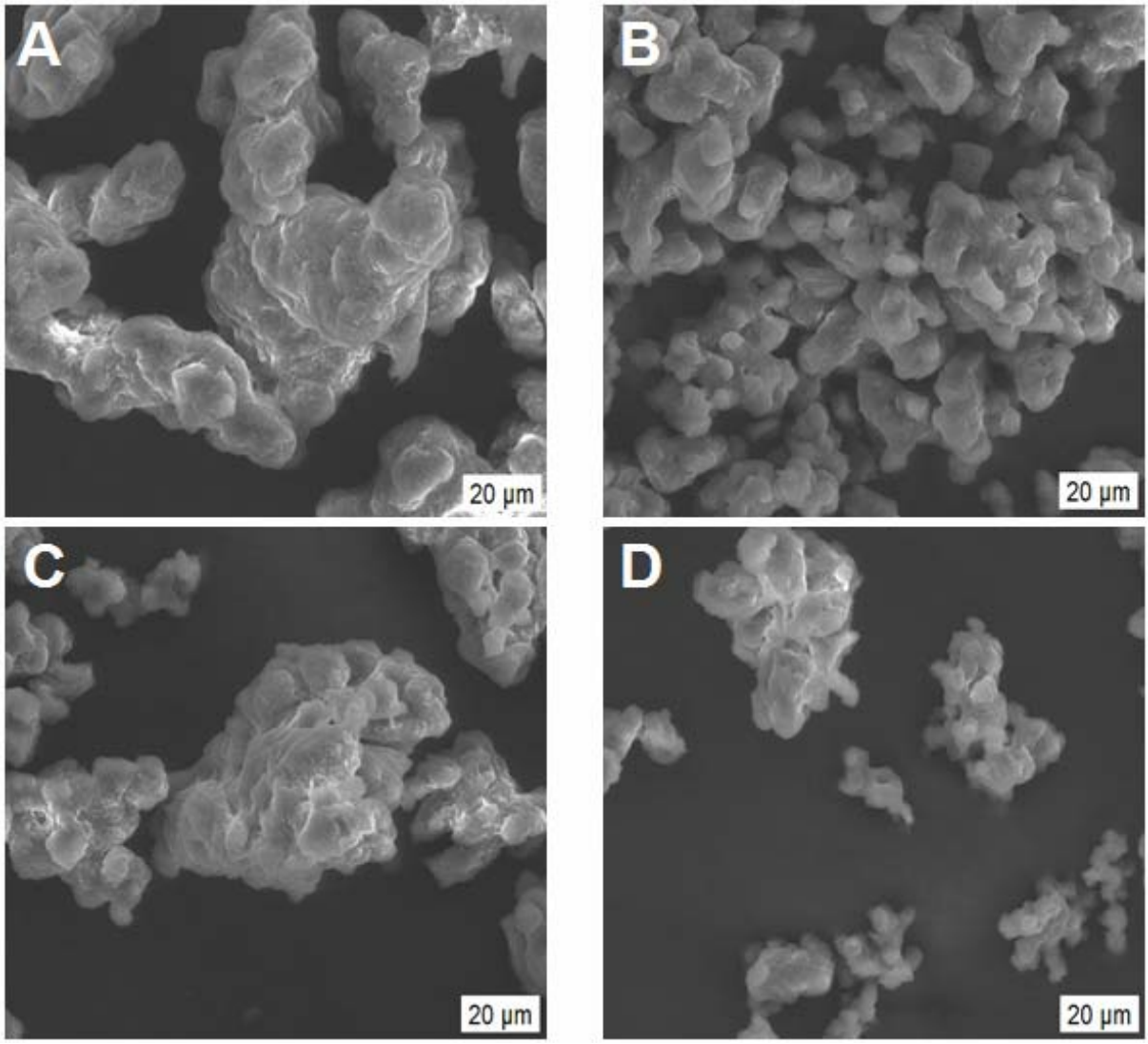

Fig. 16. SEM pictures of acetaminophen/mannitol/excipient powder mixtures containing erythritol (1/0.7/0.3) (A), maltodextrin (1/0.7/0.3) (B), erythritol (1/0.9/0.1) (C) and maltodextrin (1/0.9/0.1) (D)

Tablet capping and lamination were not observed for compacts prepared from ternary powders. As expected from the evaluation of the binary mixtures, maltodextrin had a significantly positive effect on tablet tensile strength at the highest concentration, while erythritol had a significantly negative effect on compactability (Table 8).

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

Table 8 – Tablet tensile strength (n: 10, mean ± st.dev) of reference formulation and ternary mixtures (compression force: 74 MPa)

Formulation	Tablet Tensile Strength (MPa)
Reference Formulation: Acetaminophen/Mannitol (1/1)	1.49 ± 0.21
Acetaminophen/Mannitol/Maltodextrin (1/0.9/0.1)	1.50 ± 0.30
Acetaminophen/Mannitol/Maltodextrin (1/0.7/0.3)	2.19 ± 0.21
Acetaminophen/Mannitol/Erythritol (1/0.9/0.1)	0.99 ± 0.18
Acetaminophen/Mannitol/Erythritol (1/0.7/0.1)	1.12 ± 0.14

4 Conclusions

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

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

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CHAPTER 2

MIXTURE DESIGN APPLIED TO OPTIMISE A DIRECTLY COMPRESSIBLE POWDER PRODUCED VIA CO-SPRAY DRYING

Parts of this chapter are in press:
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Abstract

A 4-component mixture containing a fixed concentration of acetaminophen and variable concentrations of mannitol, erythritol and maltodextrin was produced by co-spray drying and further processed by direct compression. Experimental design was applied to evaluate powder flowability, median particle size, density, hygroscopicity, moisture content, spray drying process yield, tablet tensile strength, friability and disintegration time. A D-optimal mixture design was constructed using a special cubic design order. The mannitol content varied between 0 and 32.55% w/w, while the erythritol and maltodextrin fraction changed from 9.3 to 41.85% w/w and from 4.65 to 23.25% w/w, respectively. 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, median particle size, powder flowability, density and hygroscopicity were negatively influenced. A combination of mannitol, erythritol and maltodextrin was suitable to improve the tablet properties of acetaminophen. Numerical optimisation was applied to determine the optimal contents for mannitol (11.6% w/w), erythritol (20.9% w/w) and maltodextrin (13.9% w/w).

Keywords: Co-spray drying; Mixture design; Acetaminophen; Carbohydrates; Compression

CHAPTER 2

MIXTURE DESIGN APPLIED TO OPTIMISE A DIRECTLY COMPRESSIBLE POWDER PRODUCED VIA CO-SPRAY DRYING

1 Introduction

In Chapter 1 co-spray drying of drug substance and carbohydrates has been applied to prepare binary and ternary spray dried powder mixtures in order to improve the physico-chemical properties (flowability, hygroscopicity and compactability) of the drug compared to its pure form. Coprocessing via spray drying of acetaminophen/carbohydrate solutions has demonstrated the efficiency of mannitol, erythritol and maltodextrin to improve the physical properties and compactability of acetaminophen. Acetaminophen/mannitol spray dried powders showed increased powder flowability, lowered moisture uptake, and resulted in tablets with an acceptable tablet tensile strength. When formulating ternary drug/carbohydrate mixtures the powder flowability and tablet tensile strength could be improved by replacing part of the mannitol fraction by erythritol or maltodextrin, respectively.

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

The goal is to optimise the ratio of the different excipients in a formulation containing acetaminophen in order to improve the physico-chemical properties of the spray dried powder and their corresponding tablet properties. Mixture design was used as the statistical tool for finding the optimal composition [1].

2 Materials and methods

2.1 Materials

Acetaminophen (median particle size: 50 µm) was received from Mallinckrodt Chemical (Hazelwood, USA). Erythritol (C*Eridex 16955) and mannitol (C*Mannidex 16700) were donated by Cerestar (Mechelen, Belgium). Maltodextrin (Glucidex® 2, DE: maximum 5) was a gift from Roquette (Lestrem, France). This maltodextrin grade consisted of 1-5% amylose and 95-99% amylopectin. Crospovidone (Kollidon® CL) was kindly donated by BASF (Ludwigshafen, 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 particles

Aqueous 4-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 demineralised 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 lab-scale Mobile Minor spray dryer (GEA NIRO, Copenhagen, Denmark). The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and 60° conical base. The solutions were fed to a two-fluid nozzle (diameter: 1 mm) at the top of the spray dryer by means of a peristaltic pump, type 520U (Watson Marlow, Cornwall, UK) and a Marprene® tube (inside diameter: 4.8 mm)(Watson Marlow, Cornwall, UK). The spray dryer operated in co-current air flow. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature, sieved (375 µm) and stored in sealed vials (room temperature, ambient relative humidity) prior to their characterisation and further use. The solutions were spray dried according to the process conditions shown in Table 2.

Table 1 – Compositions of the mixture design experiments. 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% w/w), crospovidone (6% w/w) and magnesium stearate (0.5% w/w)

Run	Components		
	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

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 Air Flow	50%

2.2.2 Experimental design

Data from Chapter 1 were used to construct the mixture design. 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 realise 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 and maltodextrin was limited to avoid a strong negative influence on tablet tensile strength and hygroscopicity, respectively.

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 design was selected [2–3].

Because interactions between the variables were expected, the following special cubic model in Eq. [1] was proposed:

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

where Y is the response, X_i, 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: 0.05) was selected, where only significant model terms were included without 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 similar correlation after ignoring the insignificant model terms, should have good agreement with predicted R^2 for the model to be fit [4]. Predicted and adjusted R^2 should be within 0.20 of each other [5]. Contour plots for the response were drawn for determination of the optimal content levels of the components.

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

2.2.3 Evaluation of spray dried powders

The flowability (n: 3)(expressed as the flowability index ff_c in 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 [6].

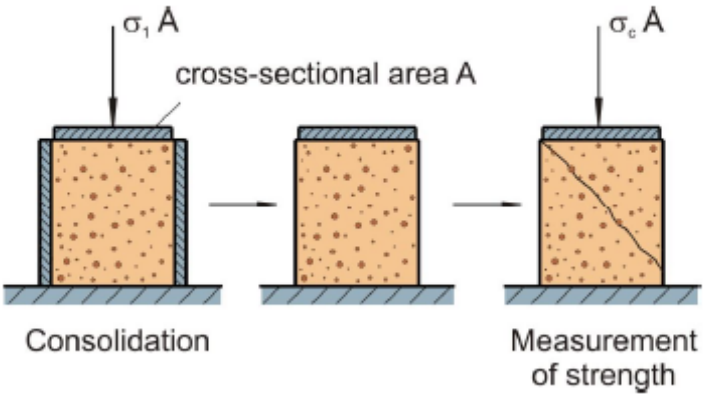

Fig. 1. Uniaxial compression test

The main goal of a shear test is to measure the compressive strength of a consolidated powder as shown in Fig. 1. This test is called a uniaxial compression test. In the first step the powder specimen, contained in a hollow cylinder with frictionless walls and cross-sectional area A, is consolidated with a consolidation stress σ_1. Then the hollow cylinder is removed and the

compressive strength is measured by pressing on top of the specimen with increasing vertical stress. The stress resulting in failure of the specimen is called the compressive strength or a confined yield strength, σ_c.

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.

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

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

The higher the consolidation stress σ_1 is, the higher is the unconfined yield strength σ_c. The ratio of the consolidation stress σ_1 to the unconfined yield strength σ_c is defined as the flowability ff_c:

A shear test a performed in two steps: in the first step, a powder sample is consolidated at a defined consolidation stress, in the second step the shear strength of the consolidated powder is measured. The difference to the uniaxial compression test is that the powder specimen is not only loaded by a static normal stress σ, but also subjected to a shear deformation (Fig. 2), for which a shear stress τ has to be applied. For consolidation, the specimen is sheared under a higher normal stress σ until the shear stress τ becomes constant. This is called “steady-state flow”. Afterwards, the consolidated sample is sheared again, but under a smaller normal stress. Thereby, the sample will “break” when a certain shear stress τ is attained (incipient flow). This way, the yield limit, called yield locus, of the consolidated powder is measured.

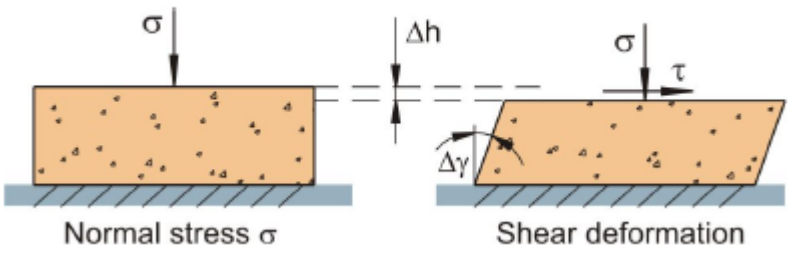

Fig. 2. Shear deformation

In Fig. 3 yield locus is drawn in a shear stress – normal stress diagram (σ-τ-diagram). The circles represent the measured points of incipient flow, the squares represent the shear and normal stresses at steady-state flow. A curve through the points of incipient flow is the yield locus, i.e. the yield limit of the consolidated sample. The large half circles represent the upper part of so-called Mohr stress circles. They represent the stresses acting in the powder in different cutting planes. The larger of the two Mohr stress circles represents the stresses at the consolidation of the powder.

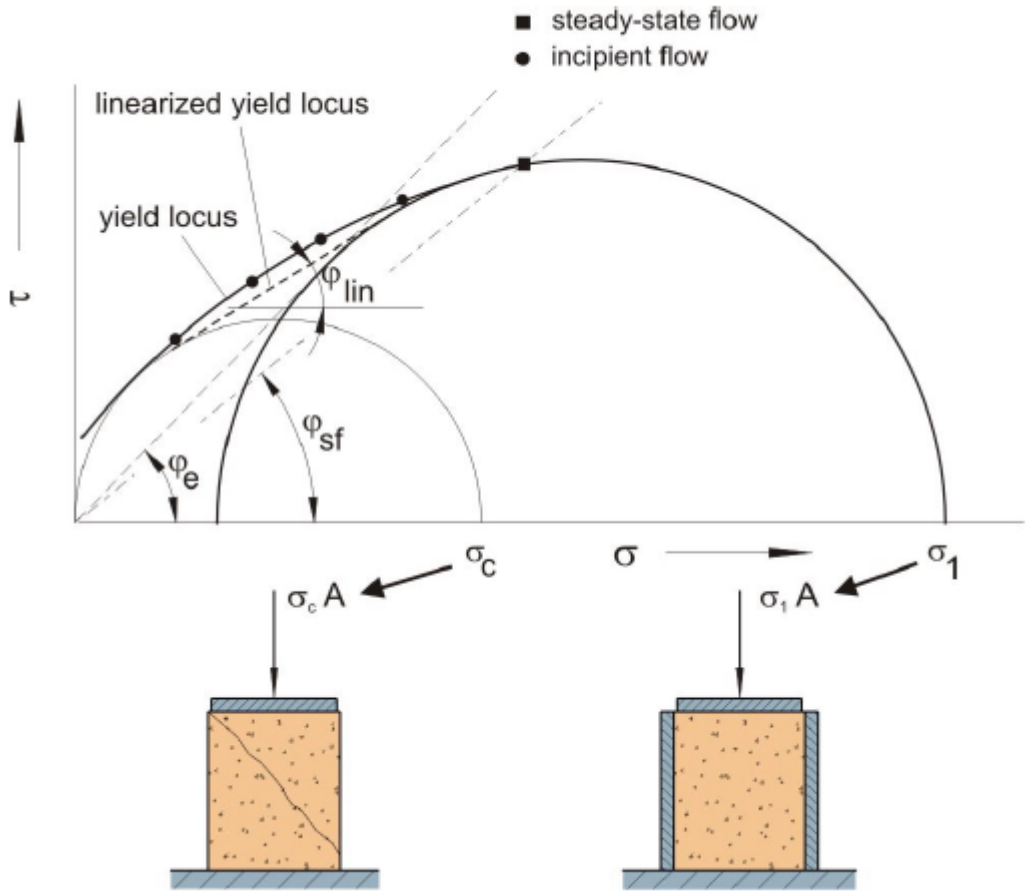

Fig. 3. Yield locus, analogy to the uniaxial compression test

The median 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). During method development jet pressure and feed rate were increased until the median particle size was constant e.g. breaking up of agglomerates in order to measure the particle size of the individual spray dried particles.

The moisture content and hygroscopic behaviour of the spray dried powders were measured and SEM pictures were recorded according to the methods described in Chapter 1 (2.2.2).

2.2.4 Tabletting process and evaluation

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 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 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.
The tablet tensile strength was measured and calculated according to the method described in Chapter 1 (2.2.3). In addition, 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 Summary statistics for the model

Analysis of variance of the responses (Table 3) indicated that response surface models developed for powder flowability, median particle size, density, hygroscopicity, tablet tensile strength, disintegration time and friability were significant and adequate, without significant lack of fit. Transformation of median particle size (power transformation, λ: 2.31) and tablet disintegration time (logarithmic transformation) responses was 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.

Table 3 – ANOVA – Influence of formulation composition on the response factors

Response factor	Model F-value	Prob>F	Lack of Fit F-value	Prob>F
Flowability	18.31	0.0002	3.31	0.1347
Median 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	St.Dev.	R^2	Adjusted R^2	Predicted R^2
Flowability	0.51	0.9105	0.8608	0.7826
Median 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

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 (Table 5) [7]. As a result, the model estimating residual moisture content was not significant.

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

Table 5 – Response results (residual moisture content, process yield, ff_c (n: 3, mean ± st.dev.), median particle size (D_{50} / span) and bulk density (n: 3, mean ± st.dev.) for mixture design experiments

Run	Responses				
	Residual Moisture Content (% w/w)	Process Yield (% w/w)	ff_c	Median 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*

3.2 Powder flowability and median particle size

Flowability index (ff_c) is a measure of the flow properties of spray dried powder mixtures. The median particle size of run 10 was classified as an outlier. Runs 4, 14, 15 with a high maltodextrin fraction (23.25% w/w) had a significantly lower flowability index and median particle size compared with formulations with a low maltodextrin fraction (4.65% w/w for runs 2, 3, 7, 11, 12, 13)(Table 5).

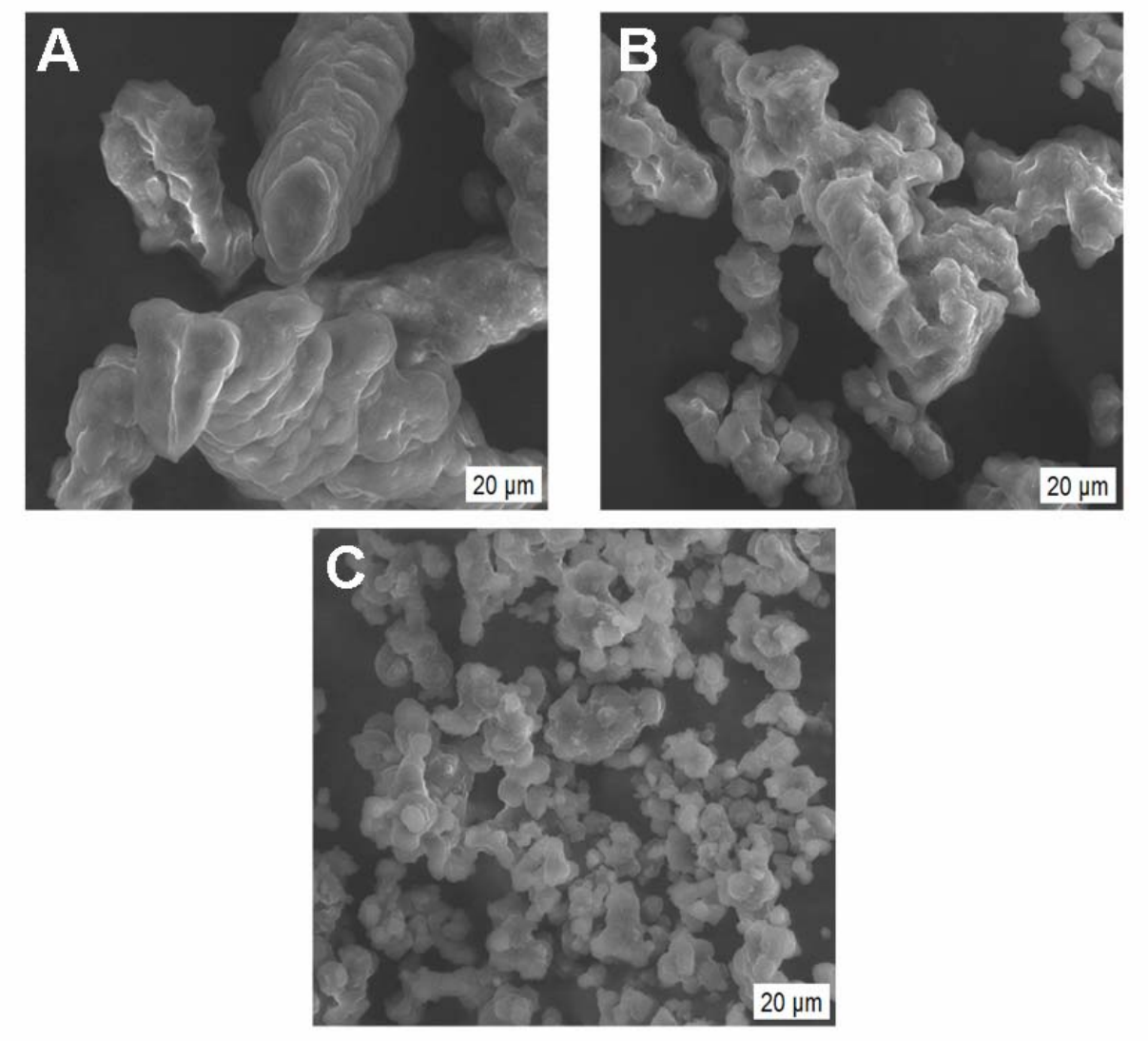

Fig. 4. SEM pictures of mixture design experiments containing 4.65% w/w (run 13), 13.95% w/w (run 6) and 23.25 % w/w (run 4) maltodextrin and a constant mannitol content

Since spray drying acetaminophen/carbohydrate solutions (1/1) containing erythritol and mannitol resulted in crystalline non-hygroscopic powders and modulated DSC experiments in

Chapter 1 showed completely amorphous maltodextrin in its corresponding co-spray dried drug/carbohydrate mixture, the formulations containing a higher maltodextrin fraction are more hygroscopic and more cohesive, resulting in poor powder flowability [8–10].

SEM pictures (Fig. 4) of formulations with increasing maltodextrin content (4.65, 13.95 and 23.25% w/w in run 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 a more spherical particle shape of the formulation containing mainly mannitol. At a high maltodextrin fraction (23.25% w/w), a decreasing erythritol concentration resulted in a higher median particle size.

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

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

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

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 and 3D surface plots based on Eq. [3] and [4] are given in Fig. 5 and 6.

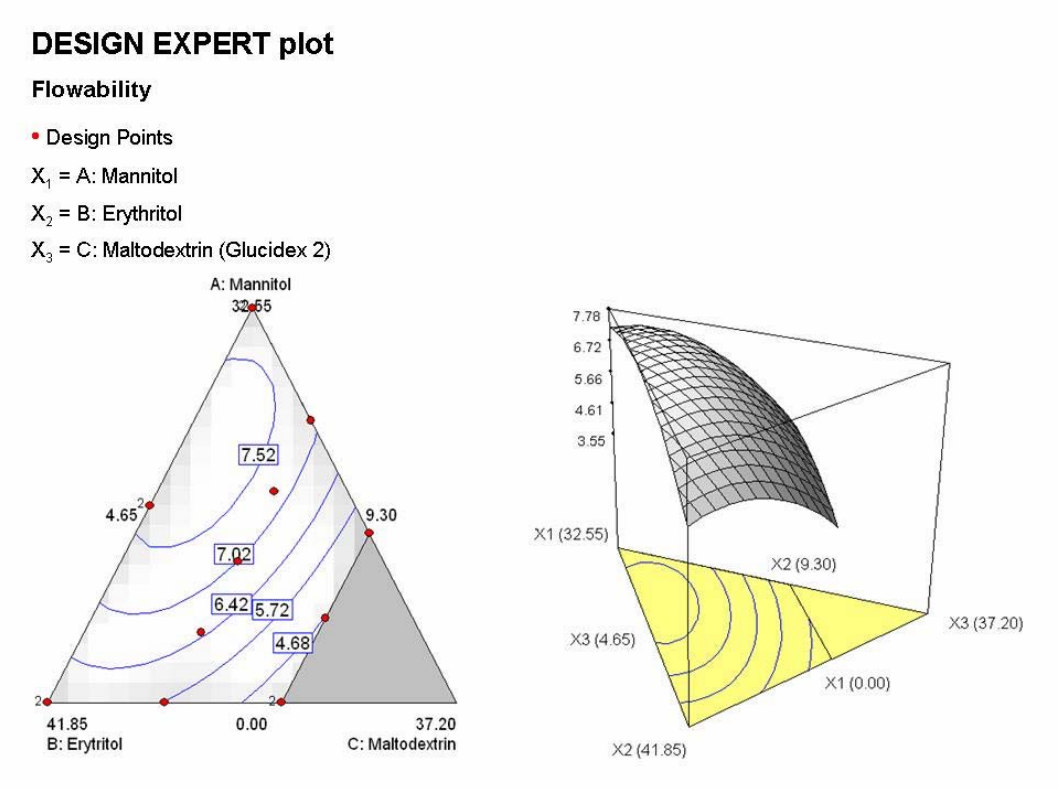

Fig. 5. Contour plot and 3D surface plot for flowability

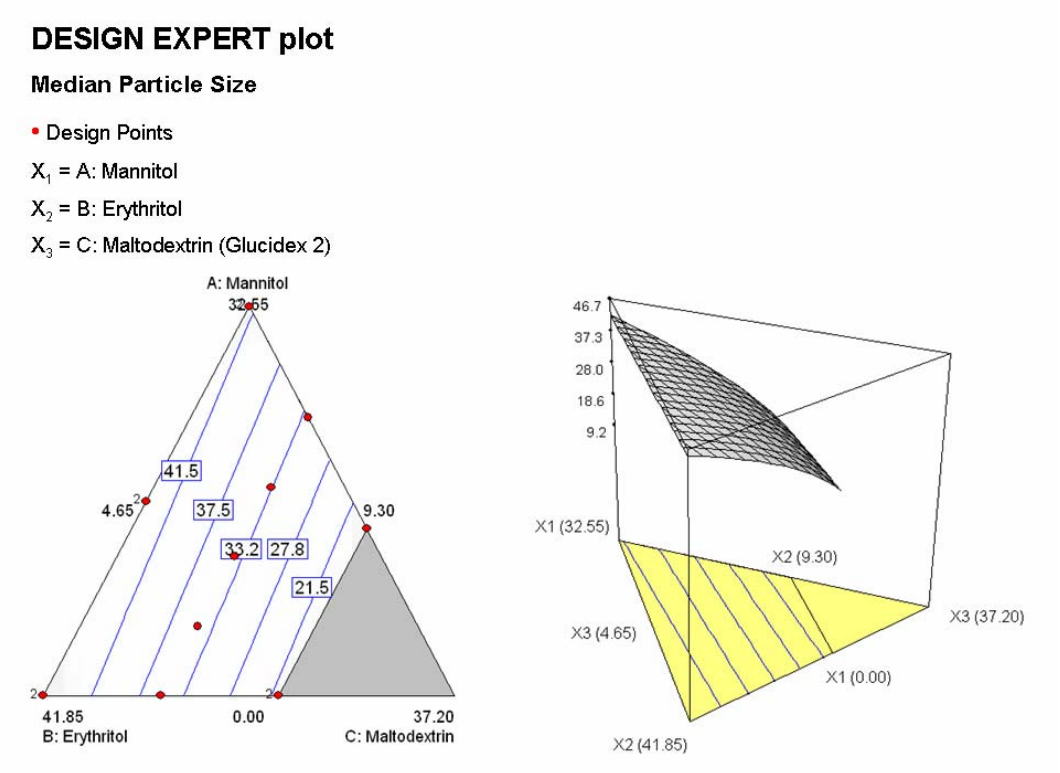

Fig. 6. Contour plot and 3D surface plot for median particle size (D_{50})

3.3 Powder bulk density

Bulk density of run 10 was classified as an outlier. Run 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 run 1, 5, 6, 8 and 9) and high (23.25% w/w for run 4, 14, 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. Similar observations were shown in Chapter 1, where co-spray dried acetaminophen/excipient mixtures (1/1) containing erythritol or mannitol had higher bulk densities in comparison with binary mixtures containing maltodextrin.

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 and 3D surface plot based on Eq. [5] are given in Fig. 7.

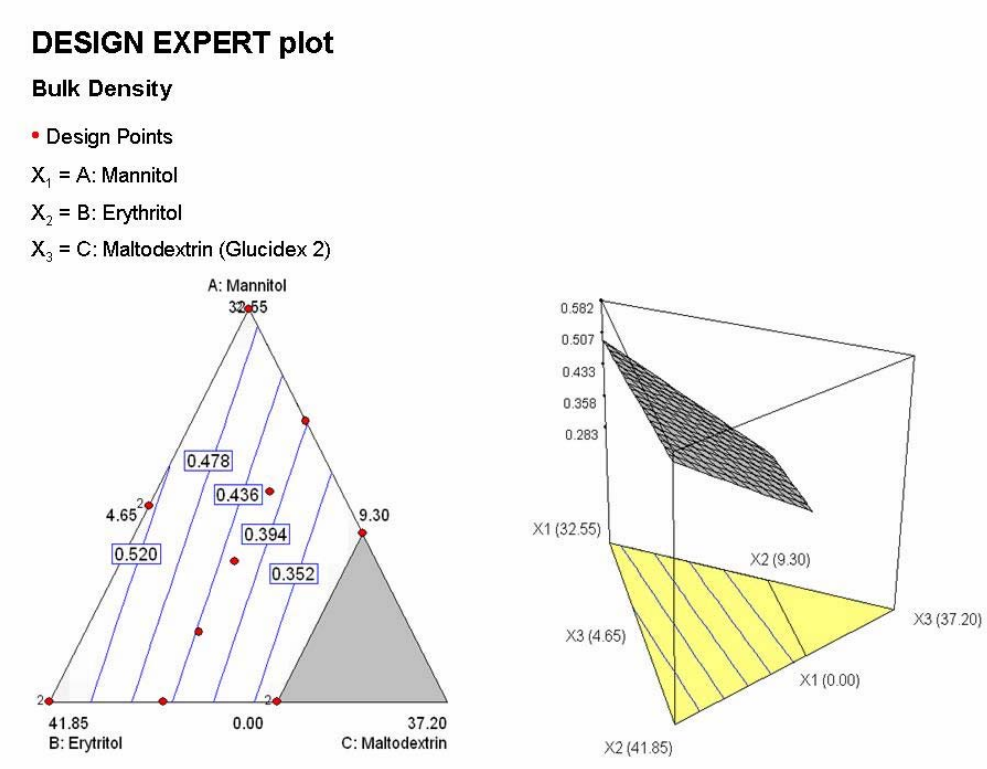

Fig. 7. Contour plot and 3D surface plot for bulk density

3.4 Powder hygroscopicity

Water uptake depended on the maltodextrin fraction due to its hygroscopic properties (Table 6). In Chapter 1 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 non-hygroscopic.

Table 6 – Response results (water uptake at 33, 52, 65, 75 and 85% relative humidity) for mixture design experiments

Run	Water uptake (%) at specific relative humidity				
	33% RH	52% RH	65% RH	75% RH	85% RH
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

Formulations containing a low maltodextrin content (4.65% w/w) had a significantly lower water uptake compared to compositions containing 13.95 or 23.25% w/w maltodextrin. At constant maltodextrin fraction the water uptake at 85% relative humidity decreased with higher erythritol contents. At 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, 52, 65, 75 and 85%) were:

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

$$WU\ (52\%\ RH) = 1.05 * A + 0.99 * B + 5.54 * C \quad (7)$$

$$WU\ (65\%\ RH) = 1.13 * A + 0.94 * B + 5.81 * C \quad (8)$$

$$WU\ (75\%\ RH) = 1.21 * A + 0.92 * B + 7.37 * C \quad (9)$$

$$WU\ (85\%\ RH) = 2.05 * A + 0.93 * B + 9.13 * C \quad (10)$$

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 and 3D surface plots based on Eq. 6, 7, 8, 9 and 10 are given in Fig. 8, 9, 10, 11 and 12, respectively.

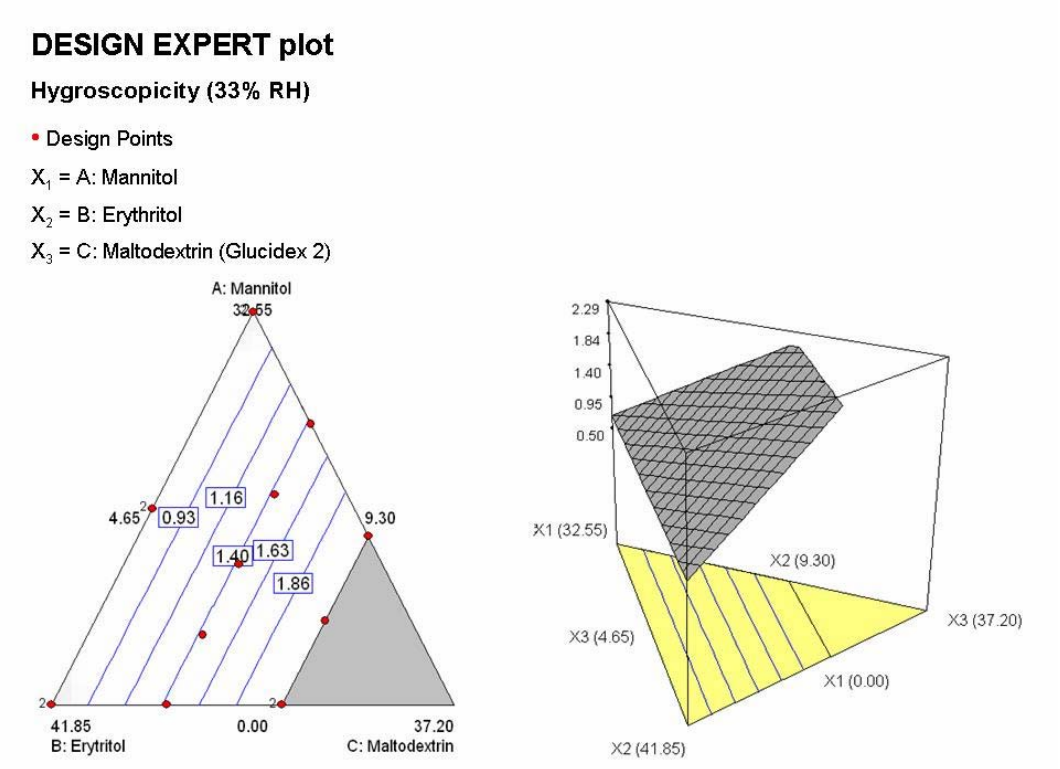

Fig. 8. Contour plot and 3D surface plot for hygroscopicity (33% RH after 2 weeks)

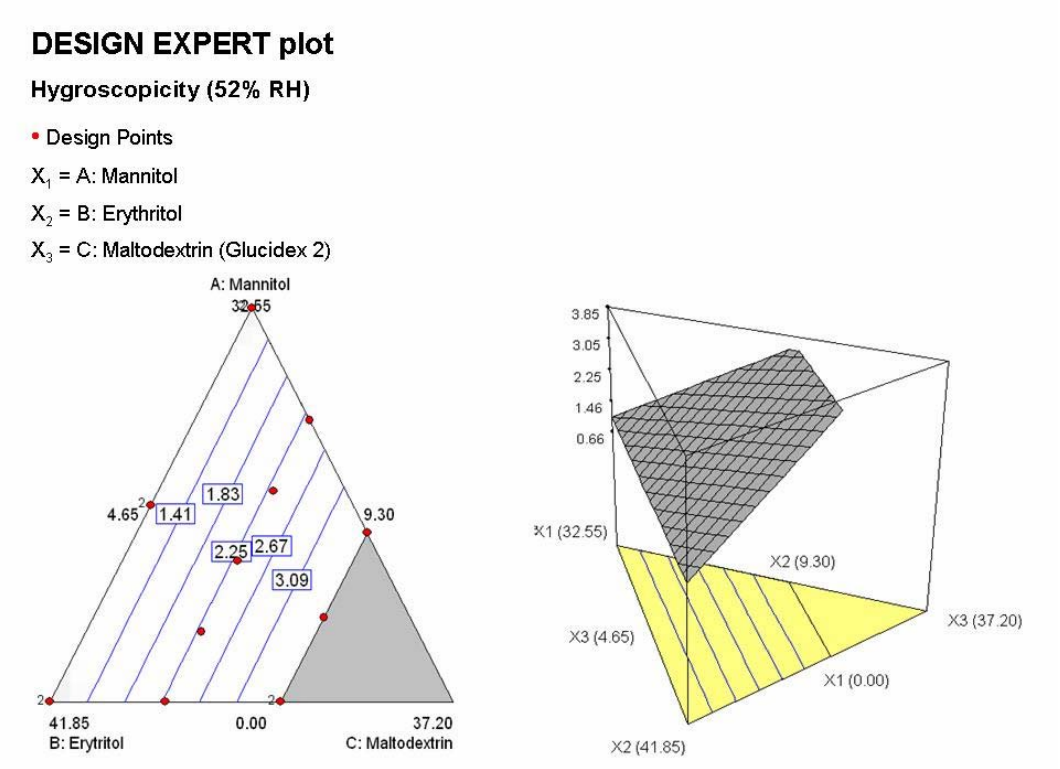

Fig. 9. Contour plot and 3D surface plot for hygroscopicity (52% RH after 2 weeks)

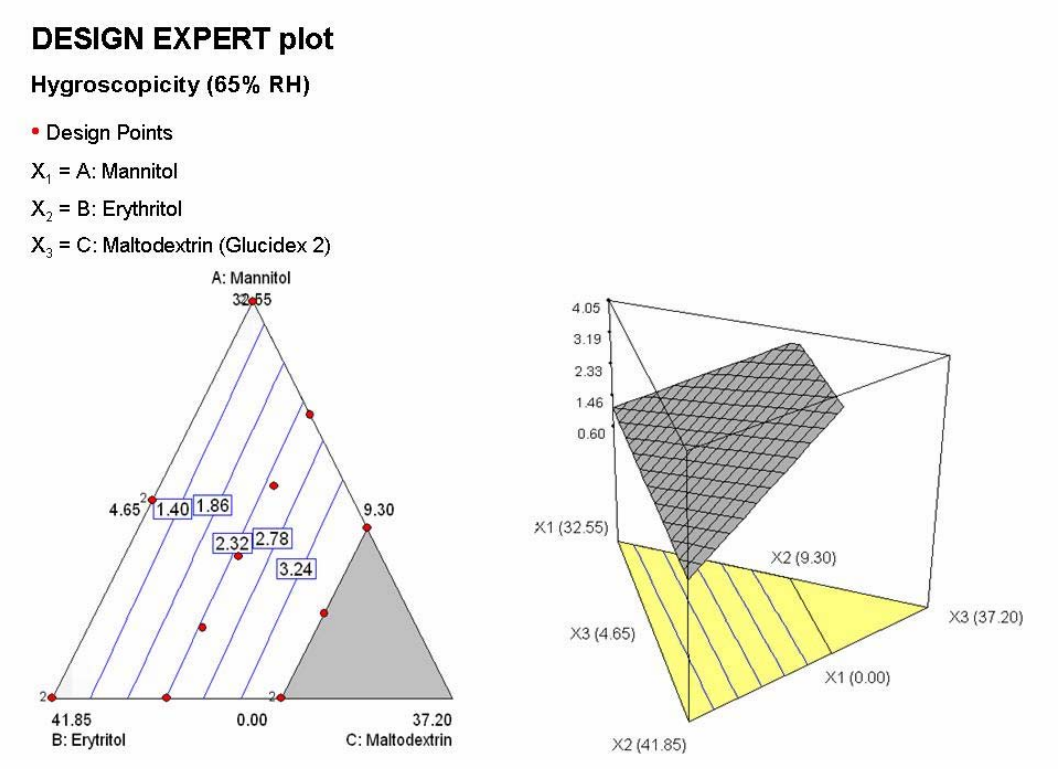

Fig. 10. Contour plot and 3D surface plot for hygroscopicity (65% RH after 2 weeks)

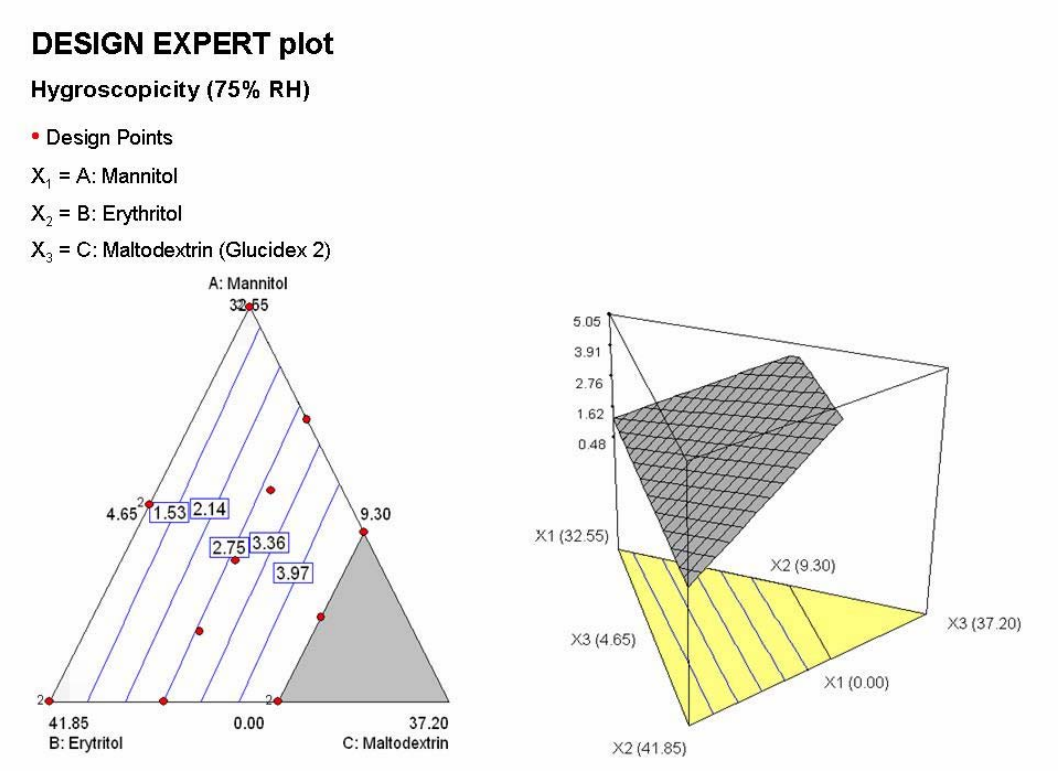

Fig. 11. Contour plot and 3D surface plot for hygroscopicity (75% RH after 2 weeks)

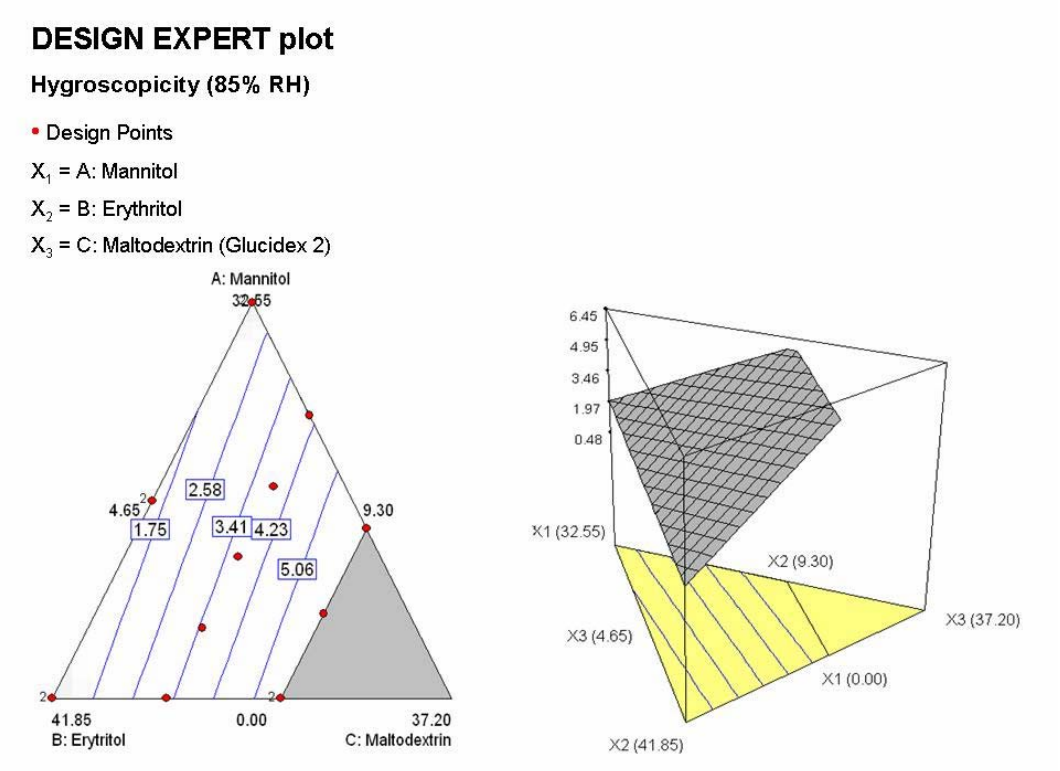

Fig. 12. Contour plot and 3D surface plot for hygroscopicity (85% RH after 2 weeks)

3.5 Tablet tensile strength, disintegration time and friability

Acetaminophen was used as model drug because of its poor compactability as evidenced by the low tablet tensile strength (0.38 and 0.67 MPa at a compression pressure of 74 MPa and 111 MPa, respectively) as well as capping and lamination problems after compaction of pure spray dried acetaminophen.

Table 7 – Response results (tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)) for mixture design experiments (compression pressure: 74 MPa)

Run	Responses		
	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 an outlier*

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 to

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 between the erythritol and mannitol content and the tablet properties. Mollan and Çelik [11–12] stated 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 which formed around the tablet on immersion into water.

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

$$TTS = 1.78 * A + 1.13 * B + 4.24 * C \quad (11)$$

$$Log_{10}(TDT) = 1.88 * A + 1.65 * B + 1.97 * C + 0.76 * AB + 4.06 * AC + 4.58\ BC \quad (12)$$

$$TF = 1.22 * A + 1.27 * B + 0.047 * C \quad (13)$$

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 and 3D surface plots based on Eq. [11], [12] and [13] are given in Fig. 13, 14 and 15, respectively.

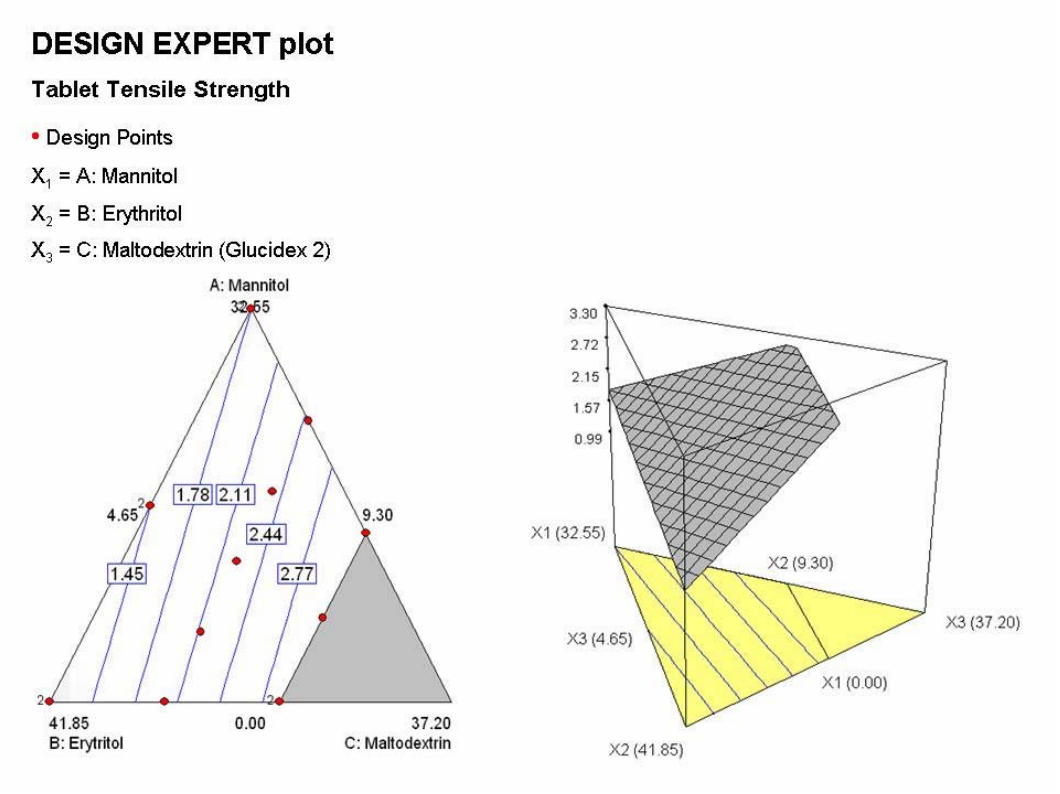

Fig. 13. Contour plot and 3D surface plot for tablet tensile strength

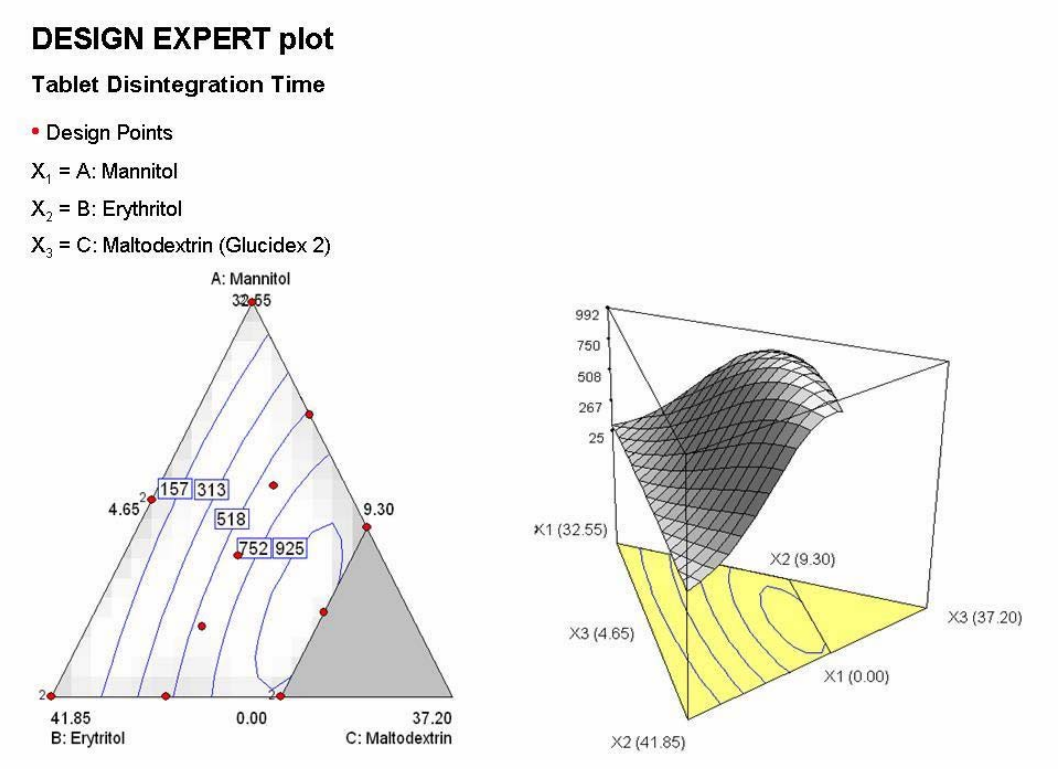

Fig. 14. Contour plot and 3D surface plot for tablet disintegration time

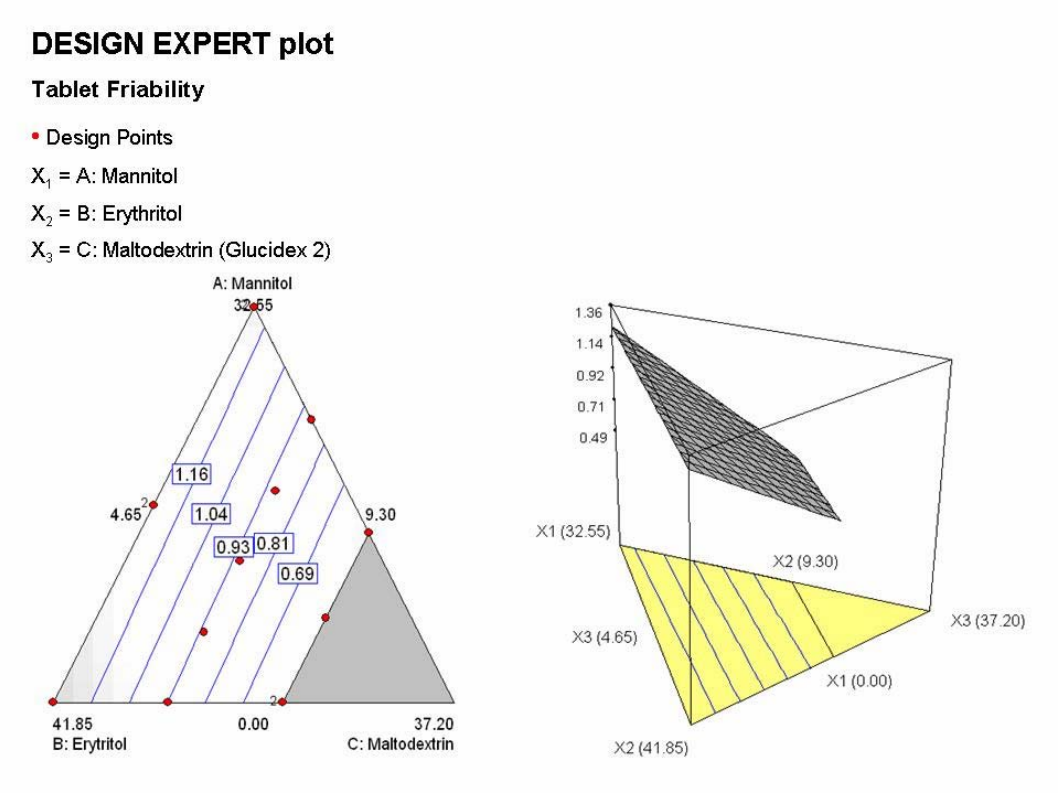

Fig. 15. Contour plot and 3D surface plot for tablet friability

3.6 Formulation optimisation and validation

Numerical optimisation was performed using statistical models to find the optimal formulation. For optimisation of the formulation the following targets were set: the flowability index and density must be higher than 7.0 and 0.400, respectively, the tablet tensile strength must be maximised while disintegration time and friability must be minimised. According to the statistical prediction the optimal formulation was:

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 (Eq. [3-13]). 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 (Table 8) of the measured responses were within in good agreement with the predicted results with exception of tablet tensile strength and disintegration time. The deviations for tablet tensile strength and disintegration time were probably caused by seasonal changes in temperature and humidity of the drying air between the period the design experiments were performed and the day the conformational experiment was conducted. These seasonal changes influenced the residual moisture content of the spray dried powder.

Table 8 – Observed responses and point prediction of the optimal formulation (Mannitol: 11.6% w/w, Erythritol: 20.9% w/w, Maltodextrin: 13.9% w/w).

	Observed	Predicted	95% Confidence Interval		95% Prediction Interval	
Response factor			Low	High	Low	High
Flowability	6.53	7.02	6.45	7.59	5.73	8.31
Median 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 at 33% RH (%)	1.45	1.42	1.26	1.59	0.77	2.08
Hygroscopicity at 52% RH (%)	2.52	2.31	2.20	2.42	1.89	2.73
Hygroscopicity at 65% RH (%)	2.76	2.40	2.28	2.52	1.93	2.87
Hygroscopicity at 75% RH (%)	2.95	2.86	2.76	2.97	2.44	3.29
Hygroscopicity at 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

4 Conclusions

Regression models were developed for powder flowability, median particle size, density and hygroscopicity. In addition, tablet tensile strength, friability and disintegration time were modelled, 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

optimisation was applied to determine the optimal contents for mannitol (11.6% w/w), erythritol (20.9% w/w) and maltodextrin (13.9% w/w).

5 References

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CHAPTER 3

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 deposition of superdisintegrant 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

CHAPTER 3

EFFECT OF MALTODEXTRIN AND SUPERDISINTEGRANT IN DIRECTLY COMPRESSIBLE POWDER MIXTURES PREPARED VIA CO-SPRAY DRYING

1 Introduction

Coprocessing of acetaminophen with carbohydrates (mannitol, erythritol, maltodextrin) improved the physical properties and compactability of acetaminophen. Formulations containing mannitol had a good flowability, low hygroscopicity and acceptable tablet tensile strength (Chapter 1). A combination of mannitol, erythritol and maltodextrin was selected for further formulation optimisation of these co-spray dried powders intended for direct compression. In Chapter 2 was stated that 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, median particle size, powder flowability, density and hygroscopicity were negatively influenced. Numerical optimisation was applied to determine the optimal contents for mannitol (11.6% w/w), erythritol (20.9% w/w) and maltodextrin (13.9% w/w).

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 [1–3]. Therefore, this research work 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 [4–6]. Based on this, the purpose 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 (median particle size: 50 μm) was received from Mallinckrodt Chemical (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). Magnesium stearate and colloidal silicon dioxide (Aerosil® 200) were purchased from Federa (Brussels, Belgium).

2.1.1 Croscarmellose sodium

Croscarmellose sodium (Ac-Di-Sol®) was donated by FMC (Brussels, Belgium). It is a water insoluble superdisintegrant for tablets [7–9], capsules [10] and granules. During wet granulation, croscarmellose sodium should be added intra- and extragranularly to make maximum use of the wicking and swelling ability of the disintegrant [11]. It has a median particle size (D_{50}) of 49 μm.

2.1.2 Sodium starch glycolate

Sodium starch glycolate (Explotab®) was received from JRS Pharma (Rosenberg, Germany). Disintegration occurs by rapid uptake of water, followed by rapid and enormous swelling [12]. Sodium starch glycolate is a water insoluble superdisintegrant incorporated in capsules and tablet formulations [13].

2.1.3 Crospovidone

Crospovidone was kindly donated by BASF (Kollidon® CL, CL-M, Ludwigshafen, Germany) or purchased from ISP (Polyplasdone® XL, XL-10, Baar, Switzerland). Median particle size, bulk and tapped density were shown in Table 1.

Table 1 – Median particle size (D_{50}), bulk and tapped density of crospovidone grades

	Median particle size (μm)	Bulk density (g/ml)	Tapped density (g/ml)
Kollidon® CL	99	0.30-0.40	0.40-0.50
Kollidon® CL-M	6	0.15-0.25	0.30-0.50
Polyplasdone® XL	107	0.21	0.27
Polyplasdone® XL-10	21	0.32	0.46

Crospovidone is a water insoluble superdisintegrant used in tablets [11, 14–15]. Due to their porous particle morphology, crospovidone particles quickly wick water into their capillaries to generate the rapid volume expansion and hydrostatic pressures that causes tablet disintegration, with little tendency to form a gel.

2.2 Methods

2.2.1 Preparation of spray dried particles

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 2.

Table 2 – Composition of the feed solution for the coprocessed formulations. 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.

	Maltodextrin Grade Selection (% of tablet composition)
Acetaminophen	46.5
Mannitol	11.6
Erythritol	20.9
Maltodextrin	14.0

In addition to the evaluation of maltodextrins, where crospovidone was physically mixed with the spray dried powder mixture, aqueous suspensions (Table 3) 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. Spray drying of these feeds was performed in lab-scale 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® tube (inside diameter: 4.8 mm)(Watson Marlow, Cornwall, UK). The spray dryer operated in co-current air flow.

Table 3 – Composition of the feed suspension for the coprocessed formulations. The ratio between the different components is expressed as a percentage of the final tablet composition

	Superdisintegrant Type and Grade Selection (% of tablet composition)
Acetaminophen	46.5
Mannitol	24.6
Erythritol	13.9
Maltodextrin	7.9
Superdisintegrant	6.0

The aqueous feeds were processed via a spray drying process, shown in Table 4. 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 4 – 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 Evaluation of spray dried powders

The moisture content and hygroscopic behaviour of the spray dried powders were measured according to the methods described in Chapter 1 (2.2.2), while the flowability, bulk density and median particle size were measured according to the methods described in Chapter 2 (2.2.3).

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 oven-dried (40°C, 2h) prior to use. After filtration these glass fiber filters were dried for 72h 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.
The tablet tensile strength was measured and calculated according to the method described in Chapter 1 (2.2.3), while tablet disintegration time and friability were measured according to the methods described in Chapter 2 (2.2.4).

3 Results and discussion

3.1 Maltodextrin grade selection

In Chapter 2 a mixture design was applied 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 2) 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). Similar to Chapter 1 the water sorption in drug/carbohydrate mixtures (ratio: 1/1) containing mannitol and erythritol

was limited, 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 [3] described that the water absorption of injection moulded starch/synthetic polymer blends decreased as the amylose content increased in the starch blends. Similarly, Ke et al. [16] 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).

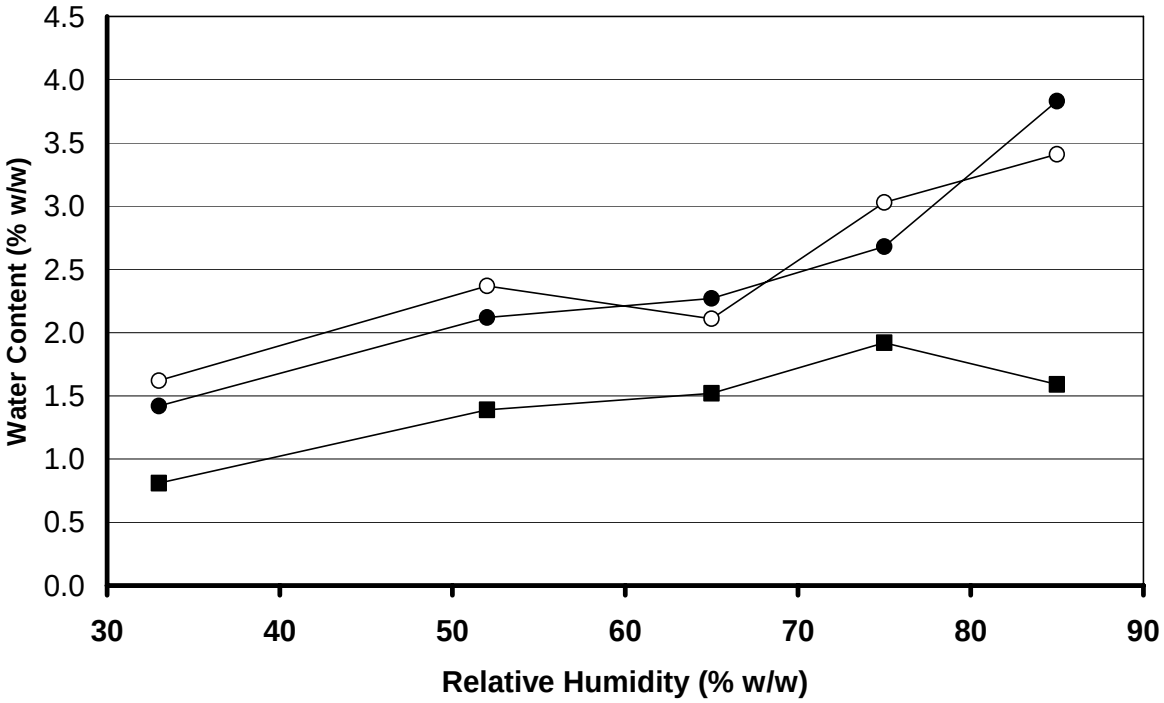

Fig. 1. Hygroscopicity of acetaminophen/mannitol/erythritol/maltodextrin powder mixtures (1/0.25/0.45/0.30) containing Glucidex® 2 (○), Glucidex® 9 (●) and Unipure DC HBA-28 (■)

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) and lower powder flowability (ff_c: 6.4 ± 0.2).
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. As stated in Chapter 2 tablet properties were mainly determined by the maltodextrin content. Tablet tensile strength and friability (Table 5) 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 5).

Table 5 – Influence of maltodextrin grade on tablet tensile strength (n: 10, mean ± st.dev.), tablet friability (n: 3, mean ± st.dev.) and tablet disintegration time (n: 6, mean ± st.dev.)
Compression pressure: 74 MPa

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

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 [17–18] 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 for disintegration of maltodextrin-containing tablets. Herman et al. [1–2] evaluated the influence of amylose/amylopectin ratio on the drug release of starch-containing tablet. A low 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 [1].

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 in Table 3. 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 [4] 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 dried insufficiently during processing to acquire dry surfaces and therefore deposited on the wall of the spray dryer. The concentration of the three superdisintegrants (Ac-Di-Sol®, Explotab®, Kollidon® CL) ranged from 20 to 77% w/w in relation to their initial content in the feed. The higher the median particle size of swollen superdisintegrant in the aqueous feed, the lower the content of superdisintegrant in the spray dried powder, resulting in lower process yields (Table 6, 7).

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 time and radial distance from the atomiser to the drying chamber wall are shorter [19]. Thus, smaller spray dryers (Mobile Minor) limit the particle size that can be successfully dried. Coarser powder from the same atomiser device can be handled in larger industrial dryers, and thus the inability to produce a desired particle specification in a lab-scale test does not automatically rule out a successful operation on a larger scale. Co-spray drying of acetaminophen, mannitol, erythritol, maltodextrin and a superdisintegrant in a production-scale spray dryer will be presented in Chapter 5.

Table 6 – Median particle size (D_{50}) of disintegrant (after swelling in an aqueous medium according to the swelling coefficients of Zhao and Augsburger [4]) and disintegrant content in spray dried powder in relation to its initial content in the feed (n: 5, mean ± st.dev.)

Disintegrant	Median Particle Size (μm)	Concentration in Spray Dried Powder (% w/w)
Ac-Di-Sol®	49.0 (96.1)	76.7 ± 5.0
Explotab®	46.4 (162.9)	20.0 ± 1.7
Kollidon® CL	99.1 (127.8)	41.7 ± 6.7
Kollidon® CL-M	6.1 (7.9)	135.0 ± 5.0
Polyplasdone® XL	107.4 (138.5)	26.7 ± 8.3
Polyplasdone® XL-10	21.1 (27.2)	68.3 ± 8.3

Table 7 – Yield, residual moisture content and tablet disintegration time (n: 6, mean ± st.dev.) Compression pressure: 74 MPa

Disintegrant	Spray dried powder		Tablet Disintegration Time (min)
	Yield (% w/w)	Residual Moisture Content (% w/w)	
Ac-Di-Sol®	78.1	2.5	*
Explotab®	62.1	3.4	18.0 ± 1.7
Kollidon® CL	68.1	2.1	14.5 ± 0.5
Kollidon® CL-M	76.3	2.1	18.3 ± 0.7
Polyplasdone® XL	66.5	1.6	17.0 ± 0.7
Polyplasdone® XL-10	67.9	2.8	*

**: Tablets were not completely disintegrated within 20 min*

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 7) in combination with the specific disintegration mechanisms. In contrast, the concentration of Kollidon® CL-M in relation to its initial concentration in the feed was 135% because of the improved drying of the micronised crospovidone particles (median particle size after swelling in an aqueous medium according to the swelling coefficients of Zhao and Augsburger [4]: 7.9 μm) in comparison with the spray dried particles formed in the drying chamber.

Tablet disintegration is based on mechanisms including water wicking, swelling, deformation recovery, repulsion and heat of wetting, and is dependent on the median particle size, porosity, swelling capacity, rate and extent of water uptake [4]. 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 [5]. Despite their high hydration capacities [4] 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 7). Kornblum and Stoopak [20] 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 median 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 7). Although the loss of crospovidone during co-spray drying depended on their median 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 median particle size, porosity, swelling capacity, rate and extent of water uptake of the disintegrant [4].

It has been reported in literature that larger disintegrant particles are more efficient than smaller particles of the same material due to a difference in swelling pressure [21]. Although the coarse crospovidone grades (Kollidon® CL and Polyplasdone® XL) had a similar median particle size (99 versus 107 µm, respectively), formulations containing Kollidon® CL resulted in a faster tablet disintegration because of the higher disintegrant concentration 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 median particle size and thus disintegration potential [14], 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 physico-chemical powder properties, tablet tensile strength and friability, while Kollidon® CL minimised tablet disintegration time.

Co-spray drying of acetaminophen, mannitol, erythritol, maltodextrin and a superdisintegrant in a lab-scale spray dryer resulted in a significant loss of superdisintegrant (related to the median size of the superdisintegrant particles after swelling in an aqueous medium) due to insufficient drying. However, coprocessing of an aqueous formulation containing superdisintegrant is probably feasible when increasing the dimensions of the spray dryer (i.e. production-scale spray dryer) since this will allow the swollen superdisintegrant particles to dry completely. This will be evaluated in Chapter 5.

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CHAPTER 4

PROCESS DESIGN APPLIED TO OPTIMISE A DIRECTLY COMPRESSIBLE POWDER PRODUCED VIA A CONTINUOUS MANUFACTURING PROCESS

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Abstract

Manufacturing of 'ready-to-compress' powder mixtures for direct compression was performed by spray drying, without granulation, milling and/or blending steps in between spray drying and compaction. Powder mixtures containing acetaminophen, mannitol, erythritol, maltodextrin, crospovidone, colloidal silicon dioxide and polyoxyethylene 20 sorbitan monooleate were prepared via co-spray drying. A feed suspension having a solid content of 27.2% w/w was selected for further process optimisation because of its high process yield, excellent flowability and short tablet disintegration time. Experimental design was applied to evaluate processibility, physico-chemical properties and compactability of the spray dried powder mixtures. Significant and adequate regression models were developed for powder flowability, median particle size, bulk density, residual moisture content and process yield. An increasing inlet and outlet drying air temperature improved process yield. However, a higher inlet drying air temperature had a negative influence on density and moisture content, while the latter decreased at higher outlet drying air temperatures. Median particle size increased with a higher inlet temperature, while the outlet temperature had the opposite affect. Numerical optimisation determined the optimal spray drying process (inlet temperature: 221°C, outlet temperature: 81°C and atomisation pressure: 6 bar) in order to produce 'ready-to-compress' powder mixtures.

Keywords: Co-spray drying; Process design; Continuous processing; Acetaminophen; Carbohydrates; Compression

CHAPTER 4

PROCESS DESIGN APPLIED TO OPTIMISE A DIRECTLY COMPRESSIBLE POWDER PRODUCED VIA A CONTINUOUS MANUFACTURING PROCESS

1 Introduction

Unlike the chemical, food, automotive and electronics industry where continuous processing has been employed for many years, conventional pharmaceutical manufacturing is generally performed using batch processing with laboratory testing conducted on collected samples to evaluate quality. The pharmaceutical industry has historically gained high profit margins and over the years limited efforts have been taken to implement time- and cost-reducing strategies and to change the manufacturing concept from batch-wise to continuous processing [1]. A change towards innovative continuous processing in the pharmaceutical industry could create regulatory uncertainty about the approval of the product. Continuous manufacturing was only able to satisfy the high quality requirements within the pharmaceutical and healthcare industry by innovative real time quality assurance using in- and on-line measurement of critical process parameters and physico-chemical properties of the manufactured goods.

Continuous processing has been preferred over batch-wise processing because of divers reasons. It reduces the time-to-market because of scale-up benefits and better quality (no batch-to-batch variations, clinical trial batches and production batches are produced on the same equipment) [1–3]. During transfer towards commercial production no bioequivalence study is demanded. Material handling is simplified since less time is required for filling, emptying and cleaning machines and a continuous process benefits from a reduced capital investment and reductions in labour costs, floor space and minimal wastage [4].

Since the traditional concept of tablet manufacturing consists of several batch-wise steps (granulation, blending, tabletting), a coprocessing technique via spray drying was developed in previous chapters to allow continuous manufacturing of ‘ready-to-compress’ mixtures, without intermediate granulation, milling or blending. Using acetaminophen as a poorly compressible drug a mixture of carbohydrates (mannitol, erythritol, maltodextrin), disintegrant (crospovidone), glidant (colloidal silicon dioxide) and surfactant

(polyoxyethylene 20 sorbitan monooleate) was selected for process optimisation of 'ready-to-compress' co-spray dried powders intended for direct compression [5–7].

The purpose of this chapter is to optimise the solid content of the feed used for co-spray drying since this increases the process capacity and minimises energy requirements, thus improving the economical profitability. Experimental design is applied to optimise the spray drying process regarding processibility, physico-chemical properties of the spray dried powder mixtures and tablet properties in order to achieve a continuous production process for solid dosage forms containing a poorly compressible drug substance. In addition, improving the manufacturing process (solid content of the feed, spray drying parameters) could improve flow properties (flowability index, density, particle size distribution, particle shape, residual moisture content).

2 Materials and methods

2.1 Materials

Acetaminophen (median particle size: 15 µm) was purchased from Atabay (Istanbul, Turkey). 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). Colloidal silicon dioxide (Aerosil® 200) was obtained from Federa (Brussels, Belgium).

2.1.1. Polyoxyethylene 20 sorbitan monooleate

Polyoxyethylene 20 sorbitan monooleate (Polysorbate 80) was purchased from Certa (Braine L'Alleud, Belgium). Polyoxyethylene sorbitan fatty acid esters are widely used as surfactants.

2.2 Methods

2.2.1 Preparation of the spray dried particles

Aqueous suspensions (Table 1) of acetaminophen, mannitol, erythritol, maltodextrin (Glucidex® 9), crospovidone (Kollidon® CL), colloidal silicon dioxide (Aerosil® 200) and polyoxyethylene 20 sorbitan monooleate (Polysorbate 80) (total solid content: 8.5, 15.7, 21.9 and 27.2% w/w) were prepared to evaluate the effect of the solid concentration of the feed. The feed suspensions were spray dried according to the process conditions shown in Table 2.

Table 1 – Composition of the feed suspension for the coprocessed formulations. The ratio between the different components is expressed as a percentage of the final tablet composition

	Concentration (% of solids content)
Acetaminophen	41.9
Mannitol	20.9
Erythritol	14.2
Maltodextrin	10.0
Crospovidone	12.0
Colloidal Silicon Dioxide	0.5
Polysorbate 80	0.5

Table 2 – Process conditions during spray drying in the Mobile Minor spray dryer (GEA NIRO)

Process Parameters	Settings
Feed Rate	Variable (g/min)
Inlet Drying Air Temperature	220°C
Outlet Drying Air Temperature	80°C
Drying Gas Rate	80 kg/h
Atomising Air Pressure	6 bar
Rotary atomiser speed	31000 rpm

In addition, aqueous suspensions (total solid content: 27.2% w/w) were subjected to a process design. The spray drying process conditions of the process design experiments are listed in

Table 3. Spray drying of these suspensions was performed in lab-scale Mobile Minor spray dryer (GEA NIRO, Copenhagen, Denmark).

Table 3 – Process parameters of the process design experiments. In addition to the variable parameters (inlet and outlet drying air temperature and atomisation pressure), each spray drying process used a drying gas rate of 80 kg/h

Run	Factors		
	A: X_1 Inlet Temperature (°C)	B: X_2 Outlet Temperature (°C)	C: X_3 Atomisation Pressure (bar)
1	200	60	6
2	170	80	6
3	170	60	5
4	215	75	5
5	215	75	4
6	170	80	6
7	170	60	6
8	230	90	6
9	170	60	4
10	170	80	4
11	200	60	4
12	170	80	4
13	205	90	6
14	180	90	5
15	200	60	6
16	230	90	5
17	205	90	6
18	230	90	4

The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and 60° conical base. In contrast with co-spray drying of aqueous solutions (batch size: 1 kg demineralised water) containing acetaminophen and carbohydrates (Chapter 1-3) via pneumatic nozzle atomisation (two-fluid nozzle), the suspensions (Table 1) 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 Marprene® tube (inside diameter: 4.8 mm) (Watson Marlow, Cornwall, UK). If the feed is an abrasive slurry of suspended solids of varying size, a rotary atomiser is more suited as a low pressure device with large flow areas and easy incorporation of wear resistant parts for prolonged trouble-free operation [8]. The spray dryer operated in co-current air flow. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature and stored (room temperature, ambient relative humidity) prior to their characterisation and further use.

2.2.2 Experimental design

Preliminary experiments were carried out to establish appropriate ranges for the processing variables. The inlet and outlet drying air temperatures varied from 170 to 230°C and from 60 to 90°C, respectively, while the atomisation pressure varied between 4 and 6 bar. The lower limits of the atomisation pressure, inlet and outlet drying air temperature were chosen to avoid process problems (low yield, sticking on the dryer wall surfaces). In addition, the difference between inlet and outlet drying air temperature was fixed at 90–140°C. A minimum of 90°C was selected to obtain an acceptable process capacity taking into account the energy loss, while a maximum difference of 140°C was set to avoid condensation in the dryer chamber. The upper limits of the inlet and outlet drying air temperature were limited to avoid a strong negative influence on powder flowability and density, while an atomisation pressure of 6 bar was the operationally maximum working condition of the rotary atomiser.

Because the experimental space is irregular, classical process designs such as the central composite or the Box-Behnken design could not be applied. Therefore, a D-optimal mixture design was selected [9–10]. Because interactions between the variables were expected, the following quadratic model was proposed Eq. (1):

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{2} \sum_{j=i+1}^{3} \beta_{ij} X_i X_j + \sum_{i=1}^{3} \beta_{ii} X_i^2 \quad (1)$$

where Y is the response, X_i, X_j are the set points of the process variables ‘i’ and ‘j’, respectively, and β_0, β_i, β_{ij} and β_{ii} are the coefficients.

The candidate points were chosen by the software (Design-Expert version 6.0.10, Stat-Ease Inc., Minneapolis, USA) and were: vertices (10), centers of the edges (15), constraint plane centroids (7), check points (10), interior points (22) and overall centroid (1). From the 65 candidate points, 10 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 18 runs. This enabled the evaluation of the appropriate regression model. Manual regression was performed. The highest order significant polynomial (significance threshold: 0.05) was selected, where only significant model terms were included without 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 [11]. Predicted and adjusted R^2 should be within 0.20 of each other [12]. 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 Evaluation of spray dried powders

The moisture content of the spray dried powders was measured and SEM pictures were recorded according to the methods described in Chapter 1 (2.2.2), while the flowability, bulk density and median particle size were measured according to the methods described in Chapter 2 (2.2.3).

The porosity of tablets composed of powder mixtures obtained via spray drying feed suspensions with different solid contents was defined using a helium gas pycnometer, Accupyc 1330 (Micromeritics, Norcross). The following analysis parameters were used: 10 purges, 10 runs and 19.5 psig as purge and run fill pressure. Final thickness and diameter of the tablets were measured with an electronic digital calliper (Bodson, Luik, Belgium).

In order to fluorescently label the amorphous phase of the spray dried particles FITC-dextran was added to the suspension at a 0.5 % w/w concentration of the maltodextrin fraction in the

suspension. The FITC-dextran was added to the solution of mannitol, erythritol, maltodextrin and polyoxyethylene 20 sorbitan monooleate and stirred until complete dissolution before the addition of acetaminophen, crospovidone and colloidal silicon dioxide. Confocal microscopy images of FITC-dextran labeled spray dried particles were recorded with a Nikon EZC1-si confocal microscope equipped with a 40x objective. Z-stacks were recorded over a total interval of 50 µm with a 1 µm step size.
The thermal behaviour and X-ray diffraction spectra of the optimised spray dried mixture were investigated using the methods described in Chapter 1 (2.2.2).

2.2.4 Tabletting process and evaluation

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 (evaluation of the solid content of the feed) or 111 MPa (process design).
The tablet tensile strength was measured and calculated according to the method described in Chapter 1 (2.2.3), while tablet disintegration time and friability were measured according to the methods described in Chapter 2 (2.2.4).

3 Results and discussion

3.1 Increasing solid content

Coprocessing of acetaminophen/carbohydrate solutions has demonstrated the efficiency of mannitol, erythritol and maltodextrin to improve the physical properties and compactability of acetaminophen (Chapter 1-2)[5–6]. Glucidex® 9 was selected as maltodextrin type because it improved tablet disintegration in combination with acceptable physico-chemical powder properties, tablet tensile strength and friability, while Kollidon® CL minimised tablet disintegration time (Chapter 3)[7]. Thus, a combination of acetaminophen, mannitol, erythritol, maltodextrin (Glucidex® 9), crospovidone (Kollidon® CL), colloidal silicon dioxide and polyoxyethylene 20 sorbitan monooleate was selected for process optimisation of 'ready-to-compress' co-spray dried powders intended for direct compression. Colloidal silicon dioxide was used as yield-increasing agent. This compound facilitates drying by its capacity

to absorb large amounts of water into its pores, thus preventing sticking of semi-wet spray dried particles to the chamber walls [13]. Polyoxyethylene 20 sorbitan monooleate was included to improve the quality of the feed suspension used for co-spray drying in case of a highly dosed poorly water soluble drug substance (preventing agglomeration of suspended particles and sticking to the container surface) and to decrease tablet disintegration time.

The flowability index (ff_c), bulk density, residual moisture content, process yield and median particle size as a function of solid content are mentioned in Table 4. Increasing the solid content of the feed had no significant influence on the flowability index, while bulk density changed significantly: at a higher solid content of the feed, a lower bulk density of the spray dried powders was obtained. Although the bulk density of spray dried powders also depends on the dimensions of the drying chamber, atomisation device, process conditions and feed composition, the lower residual moisture content and larger particle size observed for formulations processed at higher solid content contributed to the lower bulk density.

Table 4 – Influence of solid content of the feed on powder flowability, ff_c, (n: 3, mean ± st.dev.), bulk density (n: 3, mean ± st.dev.), residual moisture content, process yield and median particle size (D_{50} / span).

Solid Content (% w/w)	ff_c	Bulk Density (g/ml)	Residual Moisture Content (% w/w)	Process Yield (% w/w)	Median Particle Size (μm)
8.5	6.87 ± 0.15	0.352 ± 0.015	2.1	53.1	25.4
15.7	7.67 ± 0.31	0.338 ± 0.008	2.0	60.7	27.2
21.9	7.80 ± 0.61	0.315 ± 0.009	1.0	67.0	30.8
27.2	8.50 ± 0.89	0.326 ± 0.006	1.0	65.4	35.5

A higher solid content of the feed increased the median particle size 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 forming larger droplets. Similarly, the production of tomato powder from tomato paste showed a larger particle size at increasing solid content of the feed [14].

A higher solid content increased process yield, while residual moisture content of the spray dried powder mixtures was lowered. The atomisation of a concentrated feed suspension decreased the drying load since less water in a droplet needs to be evaporated. In addition, 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 [8]. Process yields mentioned in Table 4 are an underestimation as the duration of the spray drying experiments was limited to about 30 min. Processing a larger batch improved process yield as a large fraction of material is lost during the start-up phase before equilibrium process conditions are obtained: process yield increased from 65.4 to 84.1% when process time of a feed suspension at 27.2% solid content was extended from 31 to 84 min.

Tablet tensile strength and disintegration time decreased significantly with increasing solid content of the feed (Table 5) although at higher solid concentration (15.7–27.2% w/w) no significant difference in disintegration time was measured. The decrease in tensile strength and disintegration time was correlated with an increasing tablet porosity. Tablets with a high porosity are prone to rapid disintegration due to the fast water penetration into the porous network [15]. The tablet friability was independent of the solid content of the feed suspension.

Table 5 – Influence of solid content of the feed on tablet porosity, tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)(compression pressure: 74 MPa)

Solid Content (% w/w)	Tablet Porosity (%)	Tensile Strength (MPa)	Friability (%)	Disintegration Time (min)
8.5	18.0	1.53 ± 0.10	0.88 ± 0.08	7.0 ± 1.0
15.7	22.8	1.20 ± 0.11	1.10 ± 0.19	2.9 ± 0.1
21.9	23.4	1.05 ± 0.04	1.12 ± 0.04	2.4 ± 0.5
27.2	24.1	0.95 ± 0.06	1.19 ± 0.15	2.0 ± 0.1

A feed suspension having a solid content of 27.2% w/w was selected for further process optimisation because of its high process yield and short disintegration time in combination with excellent flow properties. SEM picture (Fig. 1) of a spray dried powder produced via coprocessing of a concentrated feed suspension (solid content of the feed: 27.2% w/w) showed large irregular agglomerates. In addition, confocal microscopy images of a spray dried particle showed agglomerates composed of individual acetaminophen crystals with a size corresponding to the average particle size of the micronised acetaminophen (D_{50}: 15 µm) (Fig. 3).

In addition, we were interested to know how if the amorphous maltodextrin compound (which acted as binder in the formulation) was distributed throughout the spray dried particles. Therefore, to visualize the amorphous phase of the spray dried particles fluorescent FITC-

dextran was added to the suspension. As FITC-dextran is an amorphous compound it will be distributed within the amorphous phase of the spay dried particles. Therefore this approach is well suited for the visualization (by fluorescence microscopy) of the distribution of maltodextrin in a spray dried particle since no other amorphous materials were detected on a DSC thermogram of a spray dried mixture (Fig. 2).

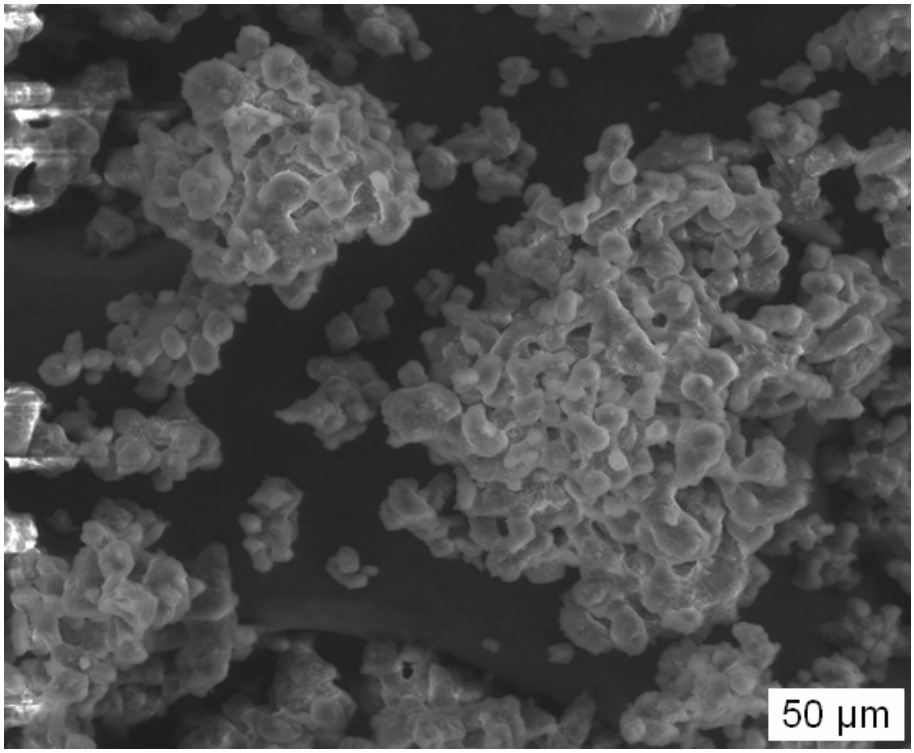


Fig. 1. SEM picture of spray dried powder (total solid content of the feed suspension: 27.2% w/w)

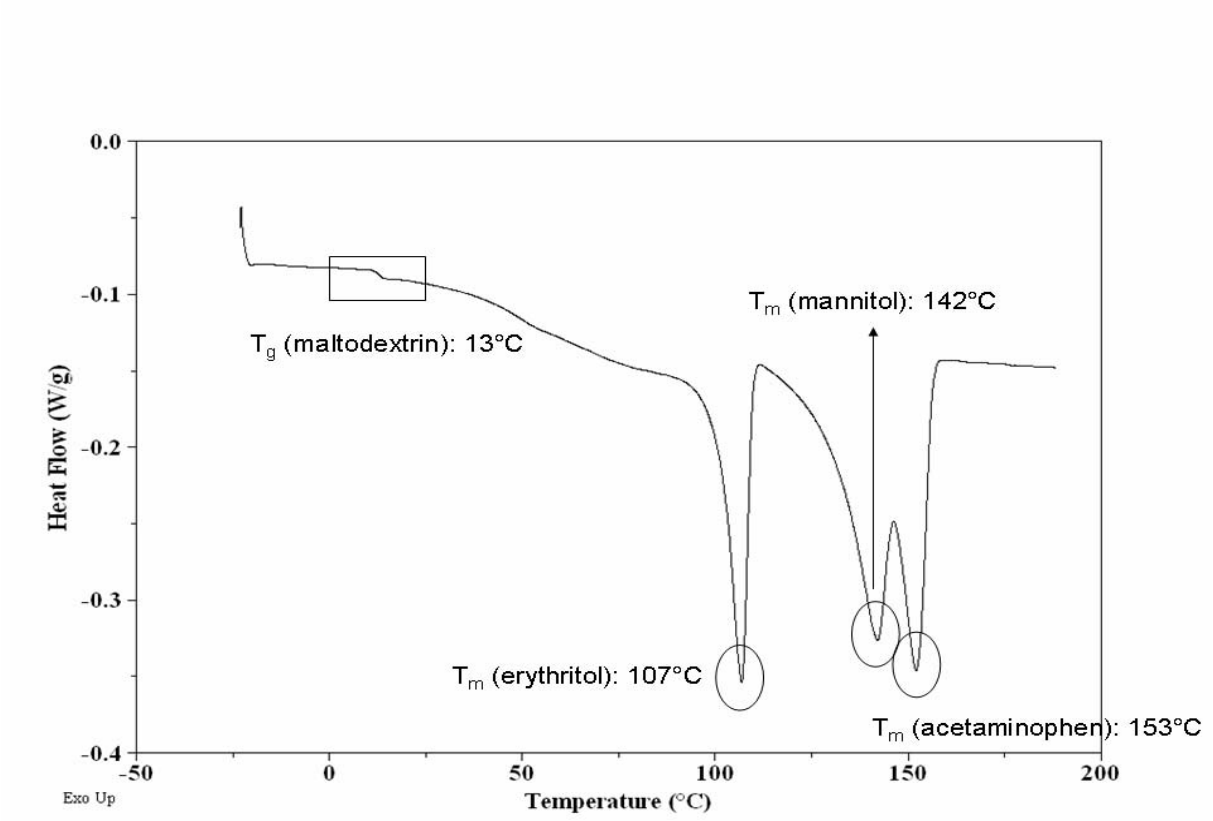


Fig. 2. Differential scanning calorimetry analysis of spray dried powder (total solid content of the feed suspension: 27.2% w/w)

Fig. 3 shows confocal images (top) of a spray dried particle composed of individual acetaminophen particles (median particle size: 15 μm) and a Z-stack (i.e. a stack of confocal images taken at different heights through the sample) of a spray dried particle (bottom). The sequence of the images is from top (0 μm) to bottom (40 μm). As can be observed the fluorescence is distributed throughout the spray dried particle, indicating that amorphous maltodextrin is spread throughout the entire spray dried particle (taking into account the variation of fluorescence at the top and bottom because of the irregular shape of the spray dried particle).

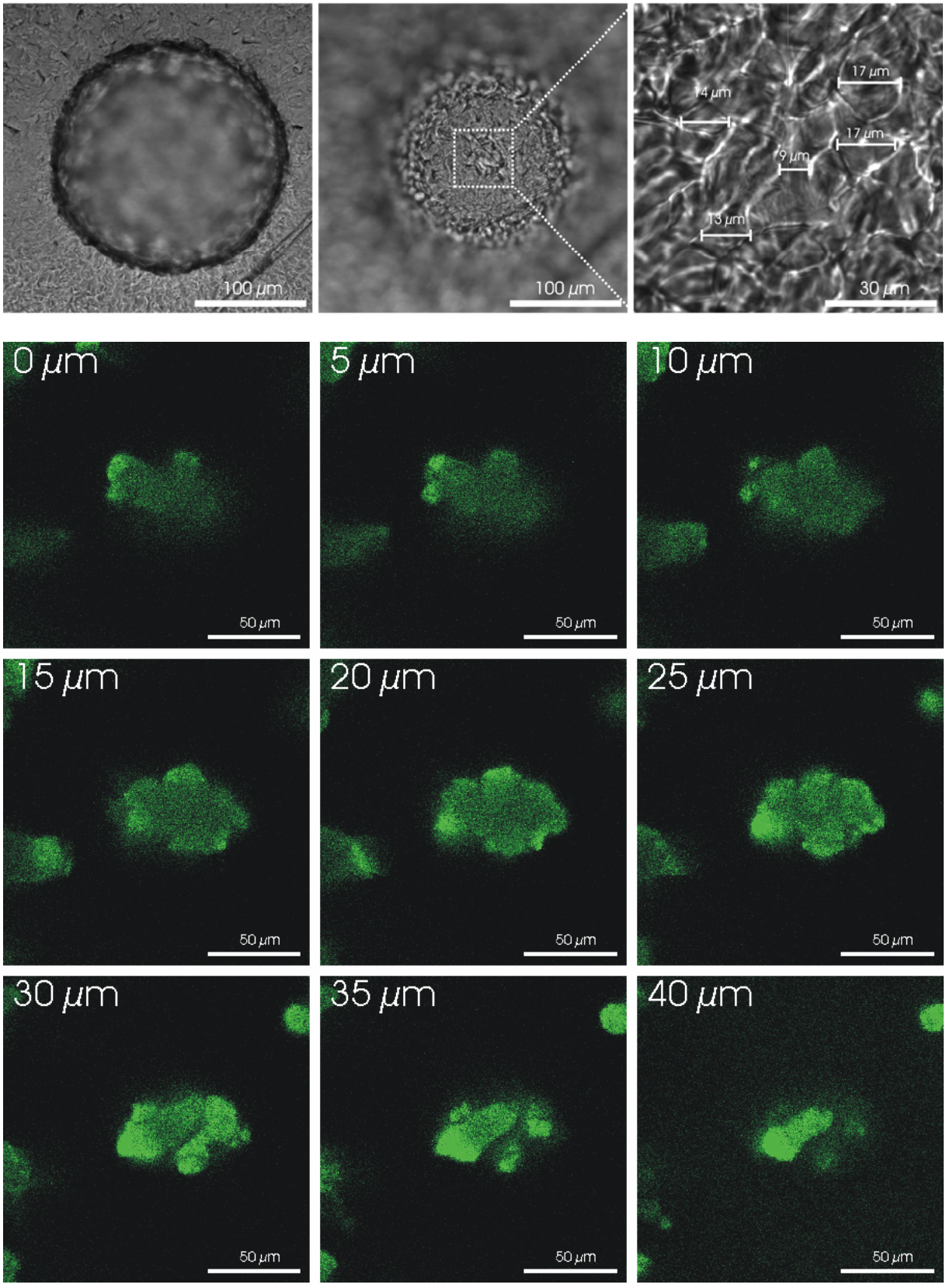


Fig. 3. Confocal microscopy images of a spray dried particle (top) and fluorescently labelled spray dried particle (bottom) (total solid content of the feed suspension: 27.2% w/w)

Fig. 4 shows the X-ray diffraction spectra of pure acetaminophen, mannitol, erythritol, maltodextrin and the spray dried powder (composition specified in Table 1). Pure acetaminophen and acetaminophen in the spray dried powder mixture were of crystalline nature as identical sharp peaks were observed in both diffraction patterns (e.g. 2θ: 18.2°, 24.3°, 26.6° and 32.8°).

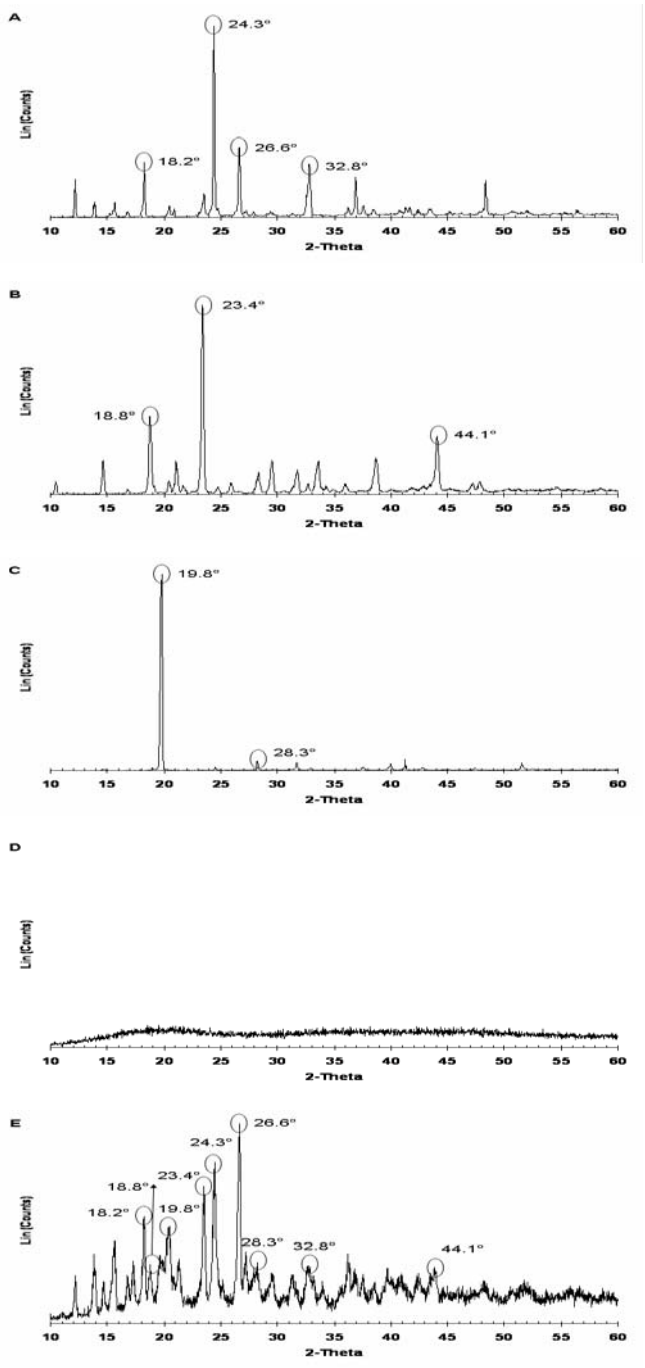


Fig. 4. X-ray diffraction patterns of acetaminophen (A) mannitol (B), erythritol (C), maltodextrin (D) and the spray dried powder mixture (total solid content of the feed suspension: 27.2% w/w) (E)

In addition, pure erythritol and mannitol were crystalline as indicated by numerous distinct peaks. The prominent peaks from pure erythritol (2θ: 19.8° and 28.3°) and pure mannitol (2θ: 18.8°, 23.4° and 44.1°) were also present in the diffraction spectrum of the spray dried powder. Maltodextrin was found to be amorphous, as indicated by the absence of diffraction peaks.

3.2 Process optimisation design

3.2.1 Summary statistics for the model

Analysis of variance of the responses (Table 6) indicated that response surface models developed for powder flowability, median particle size, density, residual moisture content process yield, tablet tensile strength, disintegration time and friability were significant, without significant lack of fit. Transformation of median particle size (power transformation, λ: -2.54) response was needed because the residuals were a function of the magnitude of the predicted values.

Table 6 – ANOVA – Influence of spray drying process variables on the response factors

Response factor	Model F-value	Prob>F	Lack of Fit F-value	Prob>F
Flowability	45.92	<0.0001	0.58	0.7798
Median Particle Size (D_{50}) (μm)	73.54	<0.0001	0.33	0.9284
Density (g/ml)	30.27	<0.0001	1.49	0.3743
Moisture Content (%)	57.99	<0.0001	0.91	0.5976
Spray Drying Yield (%)	45.92	<0.0001	0.58	0.7798
Tablet Tensile Strength (MPa)	4.21	0.0275	0.76	0.6025
Tablet Disintegration Time (s)	5.68	0.0113	0.72	0.6197
Tablet Friability (%)	4.25	0.0185	1.77	0.3029

Table 7 details the model summary statistics for the selected significant models. It can be observed that, with exception of tablet tensile strength, disintegration and friability, R^2, predicted R^2 and adjusted R^2 are in good agreement, resulting in reliable models.

Moreover, the effect of process design variables on tablet properties is not of major importance because observed tablet properties were robust since tablet tensile strength,

disintegration time and friability of all process design runs were within acceptable ranges (> 1.10 MPa, < 5 min and < 0.70%, respectively) (Table 8). Although reproducible results were obtained, the developed regression models for tablet tensile strength, disintegration time and friability did not evidence acceptable statistical measures because of limited differences in tablet properties between the different experimental settings.

Table 7 – Model Summary Statistics – Influence of spray drying process variables on the response factors

Response factor	St.dev.	R^2	Adjusted R^2	Predicted R^2
Flowability	3.36	0.9077	0.8880	0.8576
Median Particle Size (D_{50}) (μm)	1.039E-005	0.9403	0.9275	0.9012
Density (g/ml)	7.012E-003	0.8122	0.7854	0.7220
Moisture Content (%)	0.44	0.8855	0.8702	0.8376
Spray Drying Yield (%)	3.36	0.9077	0.8880	0.8576
Tablet Tensile Strength (MPa)	0.11	0.8258	0.6298	0.1163
Tablet Disintegration Time (s)	22.50	0.8647	0.7124	0.2497
Tablet Friability (%)	0.088	0.6988	0.5346	0.1499

Table 8 – Response results (tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)) for process design (compression pressure: 111 MPa)

Run	Responses		
	Tablet Tensile Strength (MPa)	Tablet Disintegration Time (s)	Tablet Friability (%)
1	1.11 ± 0.06	134 ± 9	0.58 ± 0.18
2	1.47 ± 0.04	245 ± 63	0.57 ± 0.05
3	1.84 ± 0.06	295 ± 4	0.51 ± 0.07
4	1.37 ± 0.05	218 ± 12	0.66 ± 0.02
5	1.35 ± 0.05	215 ± 9	0.68 ± 0.04
6	1.52 ± 0.08	249 ± 16	0.54 ± 0.01
7	1.50 ± 0.03	208 ± 10	0.62 ± 0.05
8	1.35 ± 0.03	194 ± 11	0.44 ± 0.09
9	1.59 ± 0.08	267 ± 26	0.50 ± 0.03
10	1.34 ± 0.04	212 ± 21	0.23 ± 0.08
11	1.15 ± 0.06	205 ± 24	0.54 ± 0.06
12	1.57 ± 0.07	220 ± 14	0.30 ± 0.08
13	1.37 ± 0.03	225 ± 22	0.36 ± 0.05
14	1.63 ± 0.06	288 ± 17	0.45 ± 0.09
15	1.31 ± 0.11	164 ± 21	0.58 ± 0.09
16	1.44 ± 0.04	241 ± 18	0.33 ± 0.11
17	1.45 ± 0.06	292 ± 14	0.55 ± 0.15
18	1.28 ± 0.04	248 ± 20	0.65 ± 0.15

3.2.2 Powder flowability

The flowability index (ff_c) is a measure of the flow properties of spray dried powder mixtures. The powder flowability of run 9 was classified as an outlier. Powder flowability is predicted by a 2-factor interaction model. Run 3 and 7 produced at low drying air temperatures (inlet temperature: 170°C, outlet temperature: 60°C) had a higher flowability index in comparison with formulations co-spray dried at high drying air temperatures (inlet temperature: 230°C, outlet temperature: 90°C for run 8, 16 and 18) (Table 9).

Table 9 – Response results (powder flowability: ff_c (n: 3, mean ± st.dev.), bulk density (n: 3, mean ± st.dev.), residual moisture content, process yield and median particle size (D_{50} / span) for process design experiments

Run	Responses				
	ff_c	Bulk Density (g/ml)	Residual Moisture Content (% w/w)	Process Yield (% w/w)	Median Particle Size (μm)
1	7.27 ± 0.15	0.314 ± 0.002	4.10	53.5	58.0 / 3.5
2	6.50 ± 1.32	0.346 ± 0.000	1.05	60.1	31.6 / 3.5
3	9.23 ± 0.55	0.372 ± 0.004 *	2.49	34.2	46.2 / 3.0
4	6.67 ± 2.06	0.315 ± 0.002	1.29	63.6	36.4 / 2.9
5	7.30 ± 0.26	0.316 ± 0.002	1.43	65.1	37.1 / 3.1
6	7.37 ± 0.29	0.350 ± 0.001	1.61	49.5	33.3 / 3.7
7	8.17 ± 0.31	0.345 ± 0.003	2.91	35.0	42.4 / 3.9
8	7.70 ± 0.36	0.313 ± 0.003	0.88	57.6	40.8 / 2.9
9	7.83 ± 0.31 *	0.328 ± 0.002	3.09	35.2	42.1 / 3.9
10	7.80 ± 0.46	0.338 ± 0.001	1.21	50.0	32.8 / 3.4
11	8.60 ± 0.85	0.313 ± 0.002	4.00	49.8	55.5 / 3.7
12	7.87 ± 0.83	0.354 ± 0.001	0.91	50.0	32.6 / 4.0
13	7.77 ± 1.07	0.319 ± 0.001	0.60	61.0	38.4 / 2.7
14	6.83 ± 0.45	0.334 ± 0.001	0.00	58.4	32.4 / 3.1
15	7.13 ± 0.15	0.316 ± 0.002	2.98	53.4	48.9 / 3.2
16	7.53 ± 0.32	0.320 ± 0.003	0.96	57.0	42.1 / 2.8
17	7.43 ± 0.21	0.315 ± 0.002	0.49	65.3	34.4 / 2.8
18	6.93 ± 0.21	0.308 ± 0.002	1.04	62.4	39.8 / 3.3

**: identified as outlier*

The fitted response surface model in terms of coded factors for the flowability index (ff_c) was:

$$ff_c = 7.41 - 0.50 * A - 0.39 * B - 0.24 * C + 0.91 * AB + 0.31 * AC + 0.47 * BC \quad (2)$$

where A is the inlet temperature, B is the outlet temperature and C is the atomisation pressure. The contour plots and 3D surface plots based on Eq. (2) are given in Fig. 5.

DESIGN EXPERT plot

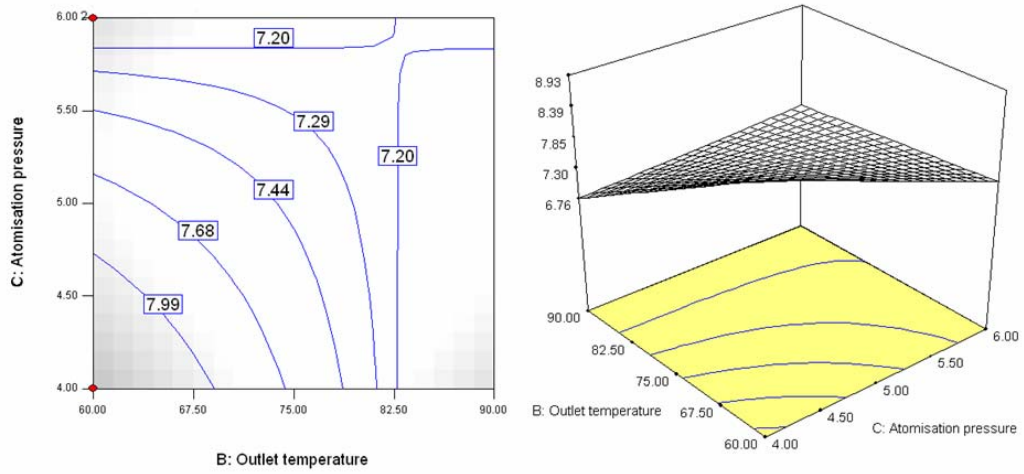
Flowability (Constant A (200°C))

• Design Points

X_1 = A: Inlet Drying Air Temperature

X_2 = B: Outlet Drying Air Temperature

X_3 = C: Atomisation Pressure



DESIGN EXPERT plot

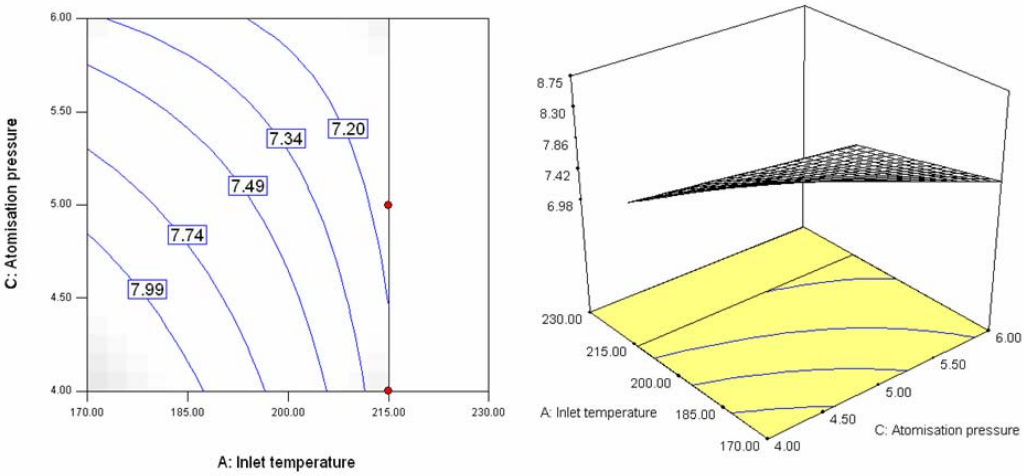
Flowability (Constant B (75°C))

• Design Points

X_1 = A: Inlet Drying Air Temperature

X_2 = B: Outlet Drying Air Temperature

X_3 = C: Atomisation Pressure



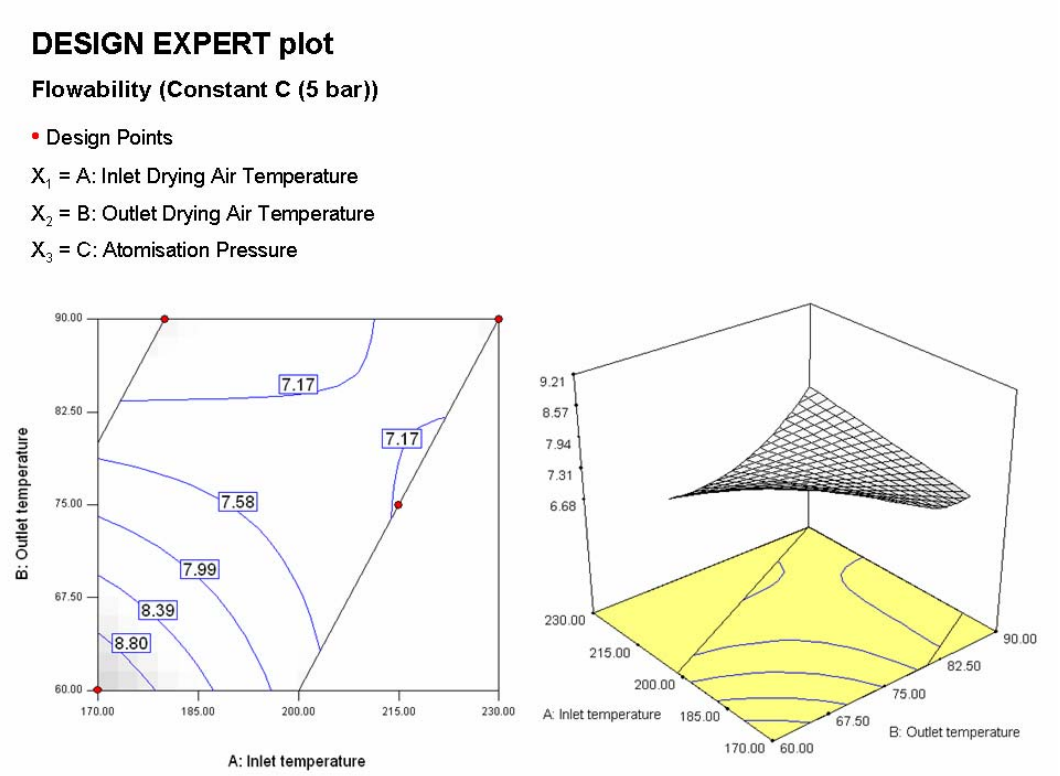


Fig. 5. Contour plots and 3D surface plots for flowability, and inlet temperature is constant at 200°C, outlet temperature is constant at 75°C and atomisation pressure is constant at 5 bar.

3.2.3 Median particle size

At constant inlet drying air temperature (170°C) the median particle size was decreased by increasing outlet drying air temperature (e.g. run 3, 7 and 9 versus run 2, 6, 10 and 12) (Table 9). In addition, coprocessing via spray drying at constant outlet drying air temperature yielded powders with larger median particle size at a higher inlet drying air temperature (run 1, 11, 15 versus run 3, 7, 9 at constant outlet drying air temperature of 60°C). Although the effect of temperature on particle size is reported to be dependent on the material being dried [16], similar observations have been made by Ståhl et al. [17] during spray drying of insulin. Broadhead et al. [18] suggested that the increase in particle size might be an effect of increased agglomeration at the higher inlet drying air temperatures due to a higher feed rate (required to obtain a constant outlet drying air temperature if the inlet drying air temperature is increased). Atomisation pressure had no significant influence on the median particle size of the spray dried powders.

The fitted response surface model in terms of coded factors for the median particle size (D_{50}) was:

$$(D_{50})^{-2.54} = 1.124E\text{-}004 - 2.750E\text{-}005 * A + 3.580E\text{-}005 * B - 3.521E\text{-}005 * B^2 \quad (3)$$

where A is the inlet temperature and B is the outlet temperature.

The contour plot and 3D surface plot based on Eq. (3) are given in Fig. 6.

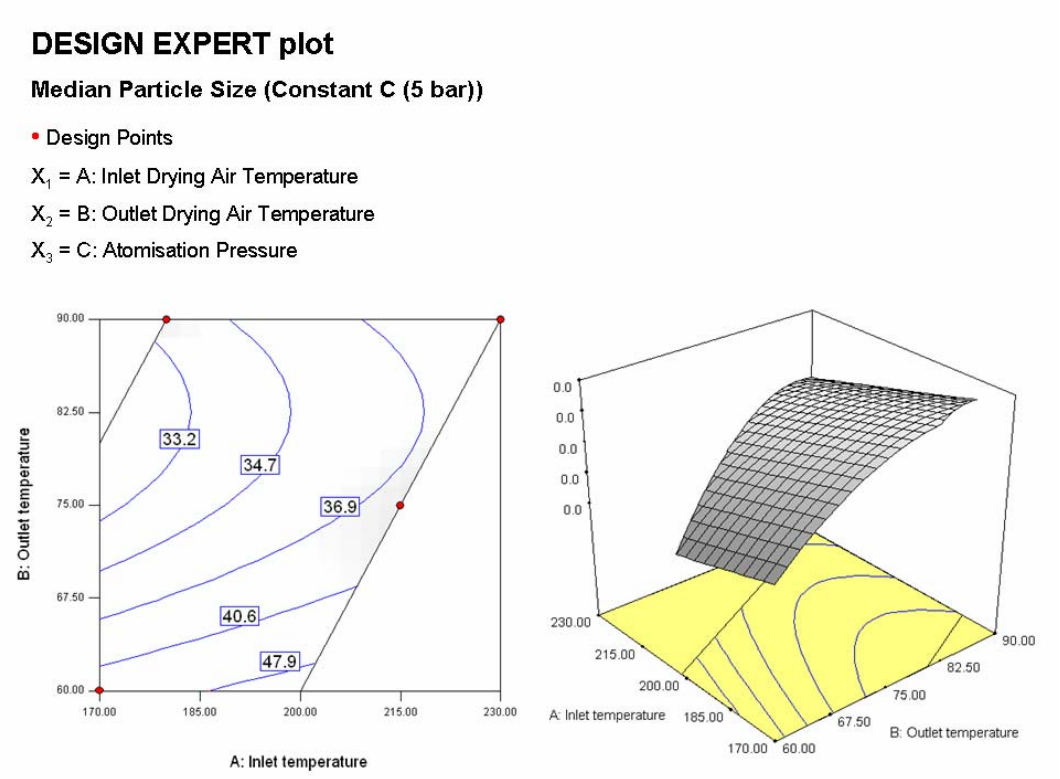


Fig. 6. Contour plot and 3D surface plot for median particle size (Atomisation pressure: 5 bar)

3.2.4 Powder bulk density

Bulk density of run 3 was classified as an outlier. Run 2, 6, 7, 9, 10 and 12 produced at an inlet drying air temperature of 170°C had a significantly higher bulk density in comparison with formulations coprocessed at medium (200°C for run 1, 11 and 15) and high (230°C for run 8, 16, 18) inlet drying air temperature (Table 9). Atomisation pressure had no significant influence on the bulk density of the spray dried powders. The decrease in bulk density with increasing inlet drying air temperature was due to case hardening of the droplet at higher temperatures followed by expansion of the entrapped air [19]. An increase in inlet drying air

temperature decreased powder bulk density for many feed formulations, but the extent was product dependent [8].

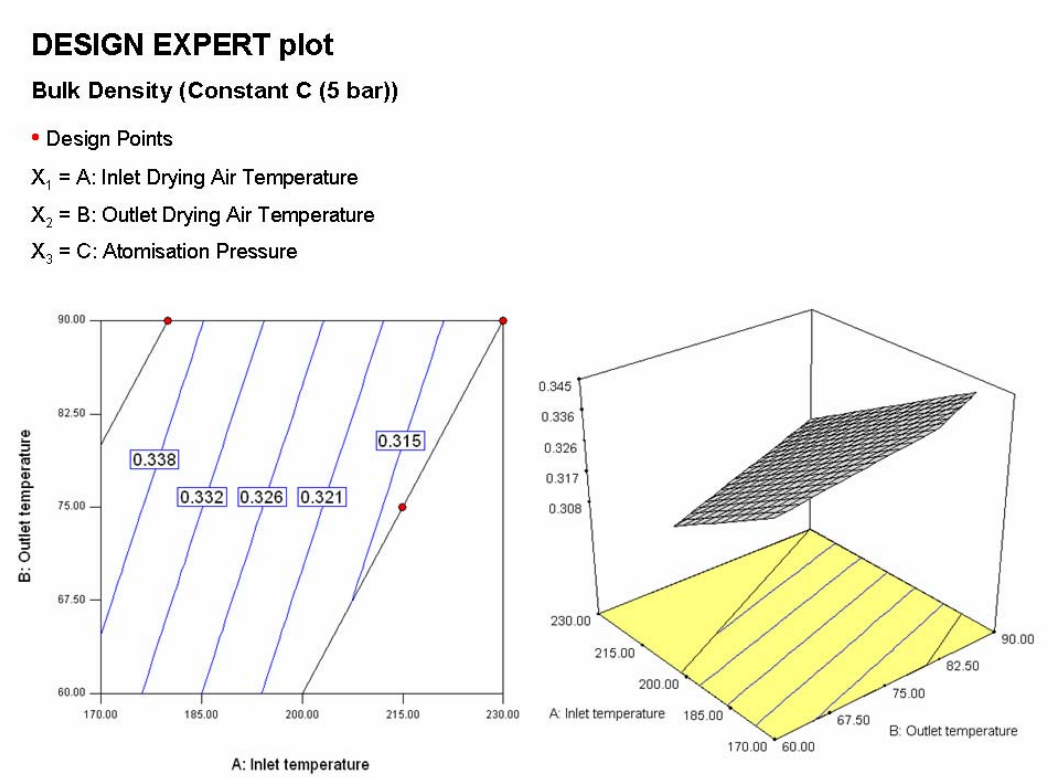


Fig. 7. Contour plot and 3D surface plot for bulk density (Atomisation pressure: 5 bar)

The fitted response surface model in terms of coded factors for the bulk density (BD) was:

$$BD = 0.32 - 0.019 * A + 5.677E\text{-}003 * B \quad (4)$$

where A is the inlet temperature and B is the outlet temperature.
The contour plot and 3D surface plot based on Eq. (4) are given in Fig. 7.

3.2.5 Residual moisture content

Runs 1, 3, 7, 9, 11 and 15 dried at low outlet drying air temperature (60°C) had significantly higher moisture contents compared with powders produced at medium (run 4 and 5) and high (run 8, 13, 14, 16, 17 and 18) outlet drying air temperature (Table 9). The high moisture content at low outlet drying temperature was often linked to agglomerated and sticky spray dried products. The small drying chamber of the Mobile Minor spray dryer used in this study

is more prone to these problems at low drying temperatures. At constant outlet drying air temperature the moisture content was increased by the inlet drying air temperature, especially at low outlet drying air temperatures (e.g. run 7 and 9 versus run 1 and 11 at an outlet drying air temperature of 60°C in comparison with run 13 and 17 versus run 8, 16, 18 at an outlet drying air temperature of 90°C). In addition, Ersus and Yurdagel [20] stated that higher drying air temperatures reduced the residual moisture content, when the difference between inlet and outlet drying air temperature was constant. Atomisation pressure had no significant influence on the moisture content of the spray dried powders.

The fitted response surface model in terms of coded factors for the residual moisture content during spray drying (RMC) was:

$$RMC = 1.89 + 0.34 * A - 1.45 * B \quad (5)$$

where A is the inlet temperature and B is the outlet temperature.

The contour plot and 3D surface plot based on Eq. (5) are given in Fig. 8.

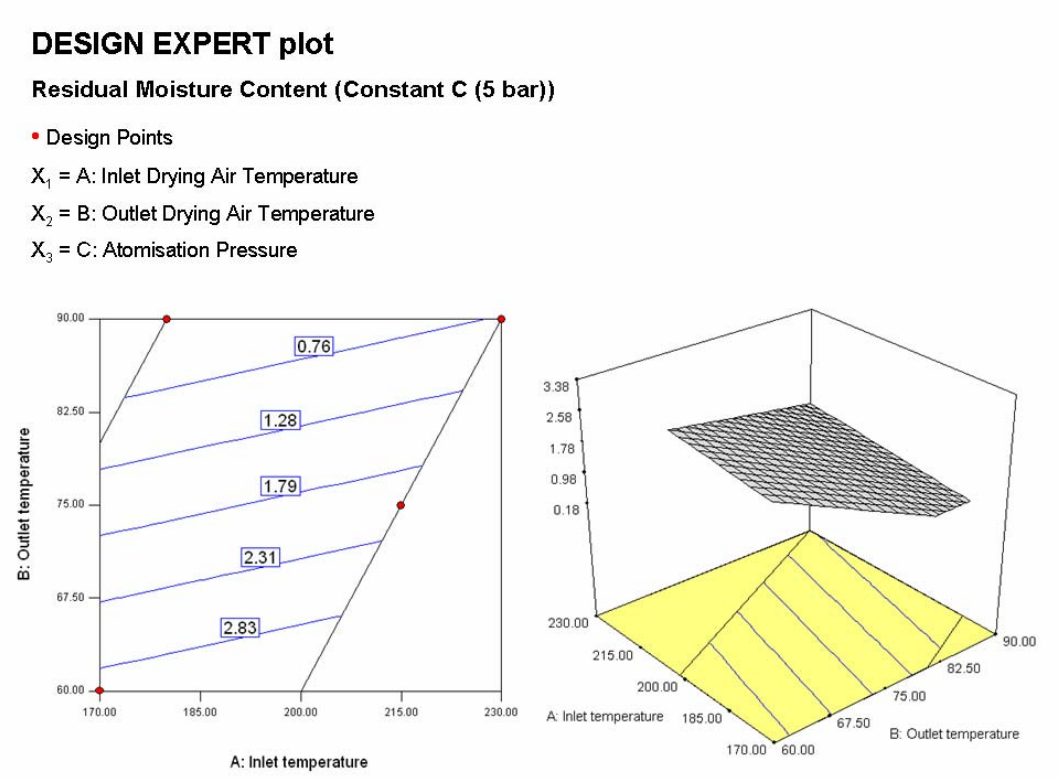


Fig. 8. Contour plot and 3D surface plot for residual moisture content (Atomisation pressure: 5 bar)

3.2.6 Spray drying yield

Formulations prepared at low outlet drying air temperature (60°C) had significantly lower process yields compared to compositions dried at higher outlet drying temperatures (80°C) using similar inlet drying air temperatures (e.g. run 3, 7 and 9 versus run 2, 6, 10 and 12 at an inlet drying air temperature of 170°C) (Table 9). At constant outlet drying air temperature (60°C) the spray drying yield increased a higher inlet drying air temperature as more thermal energy was provided for the immediate evaporation of the solvent. Broadhead et al. [18] showed that during spray drying of β-galactosidase the process yield was increased by increasing inlet drying air temperature. Similarly, spray drying of insulin for inhalation resulted in higher process yields at higher inlet drying air temperature [17]. At high outlet drying air temperature (90°C) the yield was not significantly affected by inlet drying air temperature (e.g. run 8, 13, 14, 16, 17, 18). Atomisation pressure had no significant influence on the process yield.

The fitted response surface model in terms of coded factors for the process yield (PY) was:

$$PY = 57.20 + 9.28 * A + 3.72 * B – 9.84 * AB \quad (6)$$

where A is the inlet temperature and B is the outlet temperature.
The contour plot and 3D surface plot based on Eq. (6) are given in Fig 9.

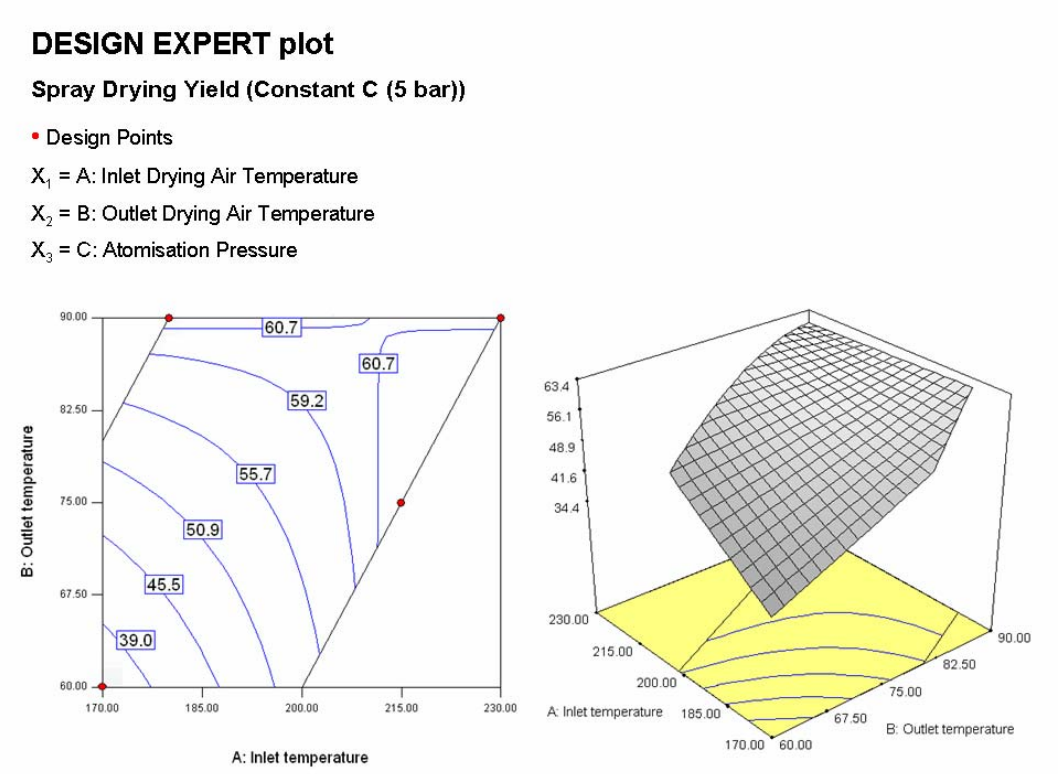


Fig. 9. Contour plot and 3D surface plot for process yield (Atomisation pressure: 5 bar)

3.2.7 Process optimisation and validation

Numerical optimisation was performed using statistical models to find the optimal spray drying process. For optimisation of the process the following targets were set: the residual moisture content must be minimised while process yield must be maximised.

According to the statistical prediction the optimal formulation process parameters were:

Inlet Temperature: 221°C
Outlet Temperature: 81°C
Atomisation Pressure: 6 bar

An experiment was performed for the selected process. In addition, point predictions were constructed by entering optimal process parameters into the current model. Design-Expert software package (version 6.0.10, Stat-Ease, Minneapolis, USA) then calculated the expected responses and associated confidence and prediction intervals (Table 10) based on the

prediction equations (Eq. [2-6]). The prediction interval has a wider spread than the confidence interval since more scatter can be expected in individual values than in averages. All the observed results (Table 10) of the measured responses were within the prediction intervals (with exception of powder flowability).

Table 10 – Observed responses and point prediction of the optimal spray drying process (Inlet temperature: 221°C, Outlet temperature: 81°C, Atomisation pressure: 6 bar)

	Observed	Predicted	95% Confidence Interval		95% Prediction Interval	
Response factor			Low	High	Low	High
Flowability (ff_c)	8.77	7.32	6.93	7.71	6.52	8.11
Median Particle Size (D_{50}) (μm)	35.44	37.30	35.73	39.16	34.19	41.73
Density (g/ml)	0.330	0.312	0.310	0.320	0.300	0.330
Moisture Content (%)	1.02	1.55	1.21	1.89	0.55	2.55
Spray Drying Yield (%)	63.09	62.4	59.74	65.12	54.74	70.11

4 Conclusions

Economic profitability was improved by increasing the solid content of the feed suspension (27.2% w/w) resulting in a high process yield, excellent flowability and short tablet disintegration time. Regression models were developed for powder bulk density, moisture content and spray drying process yield, whereas modelling of tablet hardness, friability and disintegration time was unreliable. The atomisation pressure had no significant influence on the process yield, moisture content and density. The optimised spray drying process had an atomisation pressure of 6 bar and an inlet and outlet drying air temperature of 221 and 81°C, respectively. These process settings were selected for process scale-up in order to manufacture 'ready-to-compress' powder mixtures via continuous spray drying.

5 References

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CHAPTER 5

COPROCESSING VIA SPRAY DRYING AS A FORMULATION PLATFORM TO IMPROVE THE COMPACTABILITY OF VARIOUS DRUGS

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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

CHAPTER 5

COPROCESSING VIA SPRAY DRYING AS A FORMULATION PLATFORM TO IMPROVE THE COMPACTABILITY OF VARIOUS DRUGS

1 Introduction

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 (Chapter 1–4)[1–4]. 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, Hazelwood, USA)), 2 ibuprofen-grades and cimetidine 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).

2.1.1 Ibuprofen

Two ibuprofen-grades (median particle size: 25 µm (Knoll Pharmaceuticals, Nottingham, UK) and 50 µm (BASF, Ludwigshafen, Germany)) were purchased. It has an aqueous solubility of 0.049 g/l and a melting point of 75-78°C (Martindale, The Extra Pharmacopoeia 28th Ed.). It is a highly dosed active pharmaceutical ingredient. Ibuprofen is a non-steroidal anti-inflammatory drug used to relief inflammation and pain.

2.1.1 Cimetidine

Cimetidine (median particle size: 11 µm) was purchased from Fagron (Waregem, Belgium). It has an aqueous solubility of 11 g/l and a melting point of 142°C (Martindale, The Extra Pharmacopoeia 28th Ed.). It is a highly dosed active pharmaceutical ingredient. Cimetidine is a histamine receptor antagonist and reduces the amount of acid produced by the stomach. It is used in the treatment and prevention of certain types of ulcer and gastro-oesophageal reflux.

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.

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)	31000	31000	31000

Spray drying of these suspensions was performed in lab-scale 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).

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	$Concentration_{Drug}$	70.0	75.0
Mannitol	$(93 – Concentration_{Drug}) * 0.463$	10.9	8.6
Erythritol	$(93 – Concentration_{Drug}) * 0.315$	7.4	5.8
Maltodextrin	$(93 – Concentration_{Drug}) * 0.221$	5.2	4.1
Crospovidone	6.0	6.0	6.0
Colloidal Silicon Dioxide	0.5		
Polysorbate 80	0.5	0.5	0.5

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

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
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 test 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
Residual Moisture Content (%)	2.70	0.35	0.56	0.46	0.69

The spray dried powders were cooled down to room temperature and stored (room temperature, ambient relative humidity) prior to their characterisation and further use.

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).

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

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 Table 6.

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

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

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.

Table 6 – Design runs of the central composite design experiments.

Run	Factors			
	Acetaminophen		Ibuprofen	
	A: X_1 Solid Content of the Feed (% w/w)	B: X_2 Content of Drug Substance (% w/w)	A: X_1 Solid Content of the Feed (% w/w)	B: X_2 Content of Drug Substance (% w/w)
1	32.5	45.0	26.5	49.4
2	27.2	66.3	30.0	60.0
3	37.8	66.3	30.0	60.0
4	32.5	57.5	30.0	45.0
5	40.0	57.5	25.0	60.0
6	37.8	48.7	33.5	70.6
7	32.5	70.0	35.0	60.0
8	32.5	57.5	30.0	60.0
9	32.5	57.5	33.5	49.4
10	25.0	57.5	30.0	75.0
11	27.2	48.7	26.5	70.6
	Cimetidine			
1	37.8	48.7		
2	32.5	45.0		
3	27.2	48.7		
4	25.0	57.5		
5	32.5	57.5		
6	32.5	70.0		
7	37.8	66.3		
8	32.5	57.5		
9	32.5	57.5		
10	27.2	66.3		
11	40.0	57.5		

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 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 [5]. Predicted and adjusted R-squares should be within 0.20 of each other [6]. 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 Evaluation of spray dried powders

SEM pictures were recorded according to the methods described in Chapter 1 (2.2.2), while the flowability, bulk density and median particle size were measured according to the methods described in Chapter 2 (2.2.3).
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.
The thermal behaviour and X-ray diffraction spectra of the optimised spray dried mixtures were investigated using the methods described in Chapter 1 (2.2.2).
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 2h. After filtration the glass fiber

filters were dried at 40°C for 72h 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^{TM} 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 7.

Table 7 – Process conditions and tablet properties after tablet manufacturing of acetaminophen and ibuprofen spray dried powders on the rotary Modul^{TM} P tablet press (GEA Courtoy)

Process Parameters	Acetaminophen	Ibuprofen
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

The tablet tensile strength was measured and calculated according to the method described in Chapter 1 (2.2.3), while tablet disintegration time was measured according to the methods described in Chapter 2 (2.2.4). 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).

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 6 dissolution vessels, each vessel containing 1 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 (Table 8, 9, 10) [7]. As a

result, the models estimating residual moisture content of spray dried powder mixtures containing acetaminophen, ibuprofen and cimetidine were not significant.

Table 8 – Response results (powder flowability: ff_c (n: 3, mean ± st.dev.), bulk density (n: 3, mean ± st.dev.), residual moisture content, process yield and median particle size (D_{50} / span)) for co-spray dried powders containing acetaminophen

Run	Responses				
	ff_c	Bulk Density (g/ml)	Residual Moisture Content (% w/w)	Process Yield (% w/w)	Median Particle Size (μm)
1	7.93 ± 0.31	0.361 ± 0.002 *	0.69	59.9	42.5 / 2.2
2	6.30 ± 0.36	0.308 ± 0.004	0.58	76.2	21.6 / 2.3
3	6.43 ± 0.35	0.303 ± 0.002	0.50	81.3	26.1 / 2.1
4	6.67 ± 0.21	0.315 ± 0.005	0.54	72.7	30.3 / 2.2
5	6.80 ± 0.10	0.305 ± 0.001	0.59	69.2	34.9 / 2.1
6	7.20 ± 1.13	0.319 ± 0.006	0.59	62.5	44.3 / 2.1
7	5.93 ± 0.06	0.313 ± 0.006	0.40	81.9	20.0 / 2.1
8	6.73 ± 0.31	0.323 ± 0.006	1.04	75.6	28.6 / 2.1
9	7.30 ± 0.46	0.320 ± 0.001	0.69	76.6	28.5 / 2.0
10	6.73 ± 0.06	0.311 ± 0.001	1.14	73.1	24.5 / 2.2
11	7.03 ± 0.12	0.330 ± 0.005	0.79	62.8	35.0 / 2.4

**: identified as outlier*

Table 9 – Response results (powder flowability: ff_c (n: 3, mean ± st.dev.), bulk density (n: 3, mean ± st.dev.), residual moisture content, process yield and median particle size (D_{50} / span)) for co-spray dried powders containing ibuprofen

Run	Responses				
	ff_c	Bulk Density (g/ml)	Residual Moisture Content (% w/w)	Process Yield (% w/w)	Median Particle Size (μm)
1	7.90 ± 0.70	0.379 ± 0.002	0.68	65.4	29.6 / 3.0
2	6.73 ± 0.21	0.334 ± 0.002	0.31	69.4	24.5 / 2.5
3	7.00 ± 0.30	0.338 ± 0.005	0.70	70.2	24.6 / 2.4
4	7.50 ± 0.30	0.369 ± 0.001	0.50	65.9	32.2 / 2.9
5	6.43 ± 0.21	0.326 ± 0.002	0.68	64.9	23.8 / 2.5
6	5.73 ± 0.25	0.296 ± 0.004	0.31	73.2	20.5 / 2.2
7	6.67 ± 0.78	0.306 ± 0.010	0.42	74.9	25.8 / 2.3
8	6.90 ± 046	0.310 ± 0.001	0.68	68.8	25.0 / 2.4
9	7.63 ± 0.12	0.362 ± 0.004	0.63	69.7	32.0 / 2.7
10	5.73 ± 0.25	0.296 ± 0.003	0.50	70.4	19.6 / 2.2
11	5.80 ± 0.20	0.306 ± 0.001	0.30	65.9	20.9 / 2.3

Table 10 – Response results (powder flowability: ff_c (n: 3, mean ± st.dev.), bulk density (n: 3, mean ± st.dev.), residual moisture content, process yield and median particle size (D_{50} / span)) for co-spray dried powders containing cimetidine

Run	Responses				
	ff_c	Bulk Density (g/ml)	Residual Moisture Content (% w/w)	Process Yield (% w/w)	Median Particle Size (μm)
1	7.27 ± 0.35	0.309 ± 0.002	0.59	66.1	52.2 / 2.1
2	7.20 ± 0.40	0.322 ± 0.003	0.91	64.9	55.4 / 2.4
3	7.23 ± 1.03	0.323 ± 0.001	0.82	60.0	48.4 / 2.4
4	7.93 ± 0.31	0.316 ± 0.002	0.92	71.3	38.3 / 2.2
5	7.83 ± 0.57	0.307 ± 0.002	0.57	76.0	40.7 / 2.1
6	7.07 ± 0.35	0.306 ± 0.005	0.48	82.0	29.4 / 2.2
7	7.57 ± 0.29	0.317 ± 0.001	0.72	83.5	33.3 / 1.9 *
8	7.27 ± 0.29	0.297 ± 0.001	0.38	76.1	40.7 / 2.1
9	7.27 ± 0.87	0.301 ± 0.002	0.32	70.0	40.4 / 2.1
10	7.10 ± 0.36	0.304 ± 0.007	0.39	79.7	31.2 / 2.2
11	7.43 ± 0.29	0.295 ± 0.000	0.50	73.3	44.0 / 2.0

**: identified as outlier*

Analysis of variance of the responses (Table 11) indicated that for the optimisation of the acetaminophen formulation response surface models developed for powder 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.

Table 11 – 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
	St.dev.	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

In addition, the model summary statistics for the selected significant models were detailed (Table 11). 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 12) 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 and friability (not significant) 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 12 – 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
	St.dev.	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

The 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 13).

The tablet tensile strength, disintegration time and friability of the acetaminophen, ibuprofen and cimetidine formulations produced on a lab-scale spray dryer were shown in Table 14, 15 and 16, respectively.

Table 13 - 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
	St.dev.	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 14 – Response results (tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)) for formulations containing acetaminophen (compression pressure: 130 MPa)

Run	Responses		
	Tablet Tensile Strength (MPa)	Tablet Disintegration Time (s)	Tablet Friability (%)
1	1.36 ± 0.12	352 ± 10	0.90 ± 0.01
2	0.91 ± 0.12	225 ± 4	1.36 ± 0.24
3	0.89 ± 0.13	195 ± 3	1.21 ± 0.05
4	1.02 ± 0.12	256 ± 17	0.82 ± 0.07
5	1.01 ± 0.08	263 ± 19	0.92 ± 0.04
6	1.12 ± 0.09	337 ± 13	0.76 ± 0.09
7	0.84 ± 0.03	177 ± 18	1.40 ± 0.15
8	1.09 ± 0.07	263 ± 18	0.78 ± 0.07
9	1.15 ± 0.22	311 ± 7	0.63 ± 0.04
10	1.25 ± 0.20	405 ± 24	0.76 ± 0.05
11	1.39 ± 0.15	404 ± 13	0.65 ± 0.15

Table 15 – Response results (tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)) for formulations containing ibuprofen (compression pressure: 86 MPa)

Run	Responses		
	Tablet Tensile Strength (MPa)	Tablet Disintegration Time (s)	Tablet Friability (%)
1	1.45 ± 0.07	854 ± 25	0.53 ± 0.02
2	1.41 ± 0.16	769 ± 14	0.59 ± 0.06
3	1.41 ± 0.06	808 ± 44	0.48 ± 0.01
4	1.49 ± 0.07	703 ± 20	0.56 ± 0.05
5	1.36 ± 0.18	686 ± 12	0.52 ± 0.02
6	1.45 ± 0.08	568 ± 20	0.55 ± 0.04
7	1.32 ± 0.06	662 ± 22	0.46 ± 0.01
8	1.46 ± 0.07	674 ± 23	0.44 ± 0.11
9	1.31 ± 0.05	746 ± 19	0.51 ± 0.02
10	1.23 ± 0.13	563 ± 8	0.47 ± 0.10
11	1.28 ± 0.19	622 ± 36	0.48 ± 0.02

Table 16 – Response results (tablet tensile strength (n: 10, mean ± st.dev.), tablet disintegration time (n: 6, mean ± st.dev.) and tablet friability (n: 3, mean ± st.dev.)) for formulations containing cimetidine (compression pressure: 120 MPa)

Run	Responses		
	Tablet Tensile Strength (MPa)	Tablet Disintegration Time (s)	Tablet Friability (%)
1	1.45 ± 0.19	357 ± 3	0.52 ± 0.03
2	1.73 ± 0.10	375 ± 7	0.47 ± 0.04
3	1.80 ± 0.08	370 ± 6	0.50 ± 0.05
4	1.77 ± 0.09	362 ± 10	0.64 ± 0.08
5	1.64 ± 0.08	348 ± 5	0.62 ± 0.04
6	1.32 ± 0.16	281 ± 14	0.95 ± 0.08
7	1.41 ± 0.04	280 ± 10	0.81 ± 0.05
8	1.58 ± 0.13	327 ± 16	0.60 ± 0.05
9	1.51 ± 0.17	320 ± 9	0.56 ± 0.03
10	1.41 ± 0.07	330 ± 6	0.93 ± 0.07
11	1.35 ± 0.07	323 ± 5	0.67 ± 0.03

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 17, while the corresponding contour plots are given in Fig. 1–9.

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 versus 11 and run 3 versus 6 at a solid content of the feed of 27.2 and 37.8% w/w, respectively)(Table 8) as there is less mannitol and maltodextrin available in the formulation to agglomerate the suspended acetaminophen particles. At a constant acetaminophen concentration, the median particle size increased with the solid content of the feed suspension (e.g. run 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 9, 10). Similarly, in Chapter 4 a higher median particle size was measured at higher solid content of the feed suspension, while the production of tomato powder from tomato paste showed an increased median particle size at increasing solid content of the feed suspension [8].

Table 17 – 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 – 3.061E-003 * A – 8.180E-003 * B – 6.224E-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

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 [8], the specific quadratic relationship between solid content

of the feed suspension and bulk density (Table 17) resulted in an optimal bulk density (ρ: 0.321 g/ml) at a solid content of 31.2% w/w (e.g. run 10, 5 versus run 4, 8, 9 at an acetaminophen concentration of 57.5% w/w)(Table 8). 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 9).

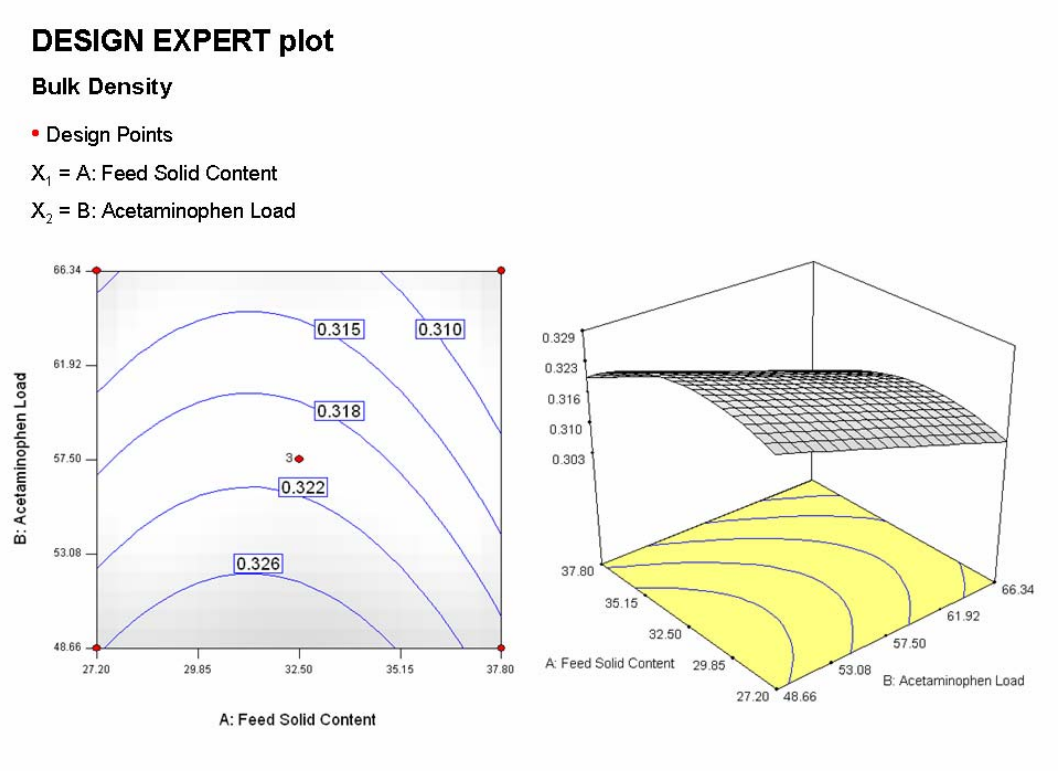

Fig. 1. Influence of solid content of the feed suspension and acetaminophen concentration on density

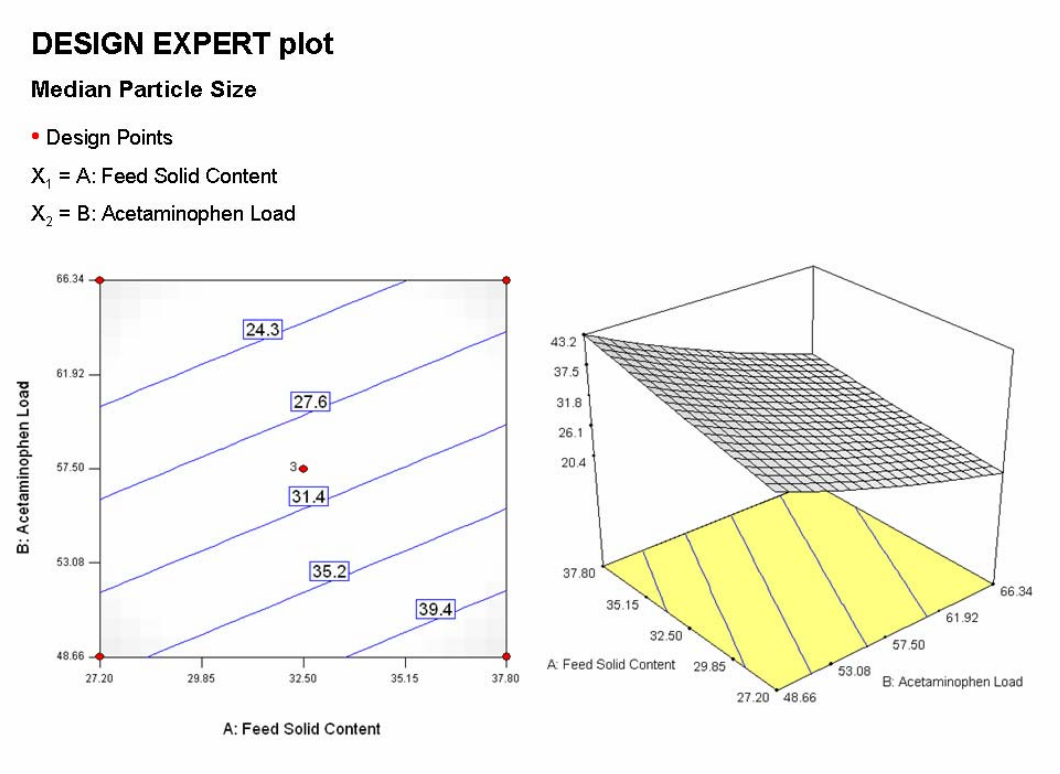

Fig. 2. Influence of solid content of the feed suspension and acetaminophen concentration on median particle size

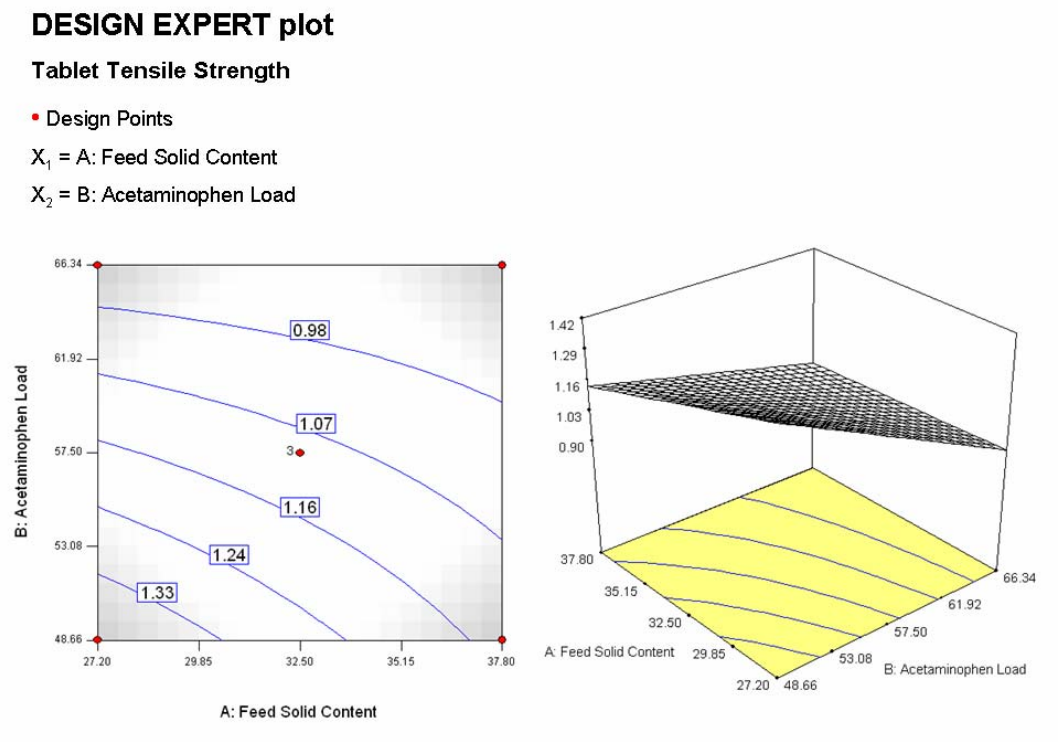

Fig. 3. Influence of solid content of the feed suspension and acetaminophen concentration on tablet tensile strength

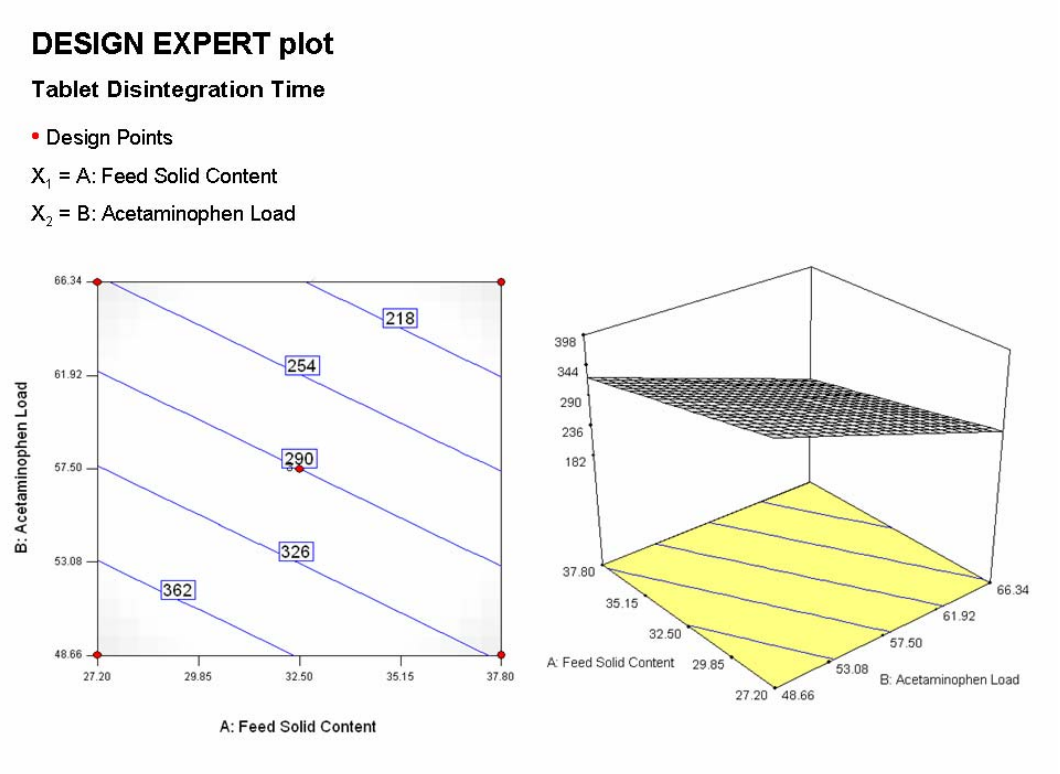

Fig. 4. Influence of solid content of the feed suspension and acetaminophen concentration on tablet disintegration time

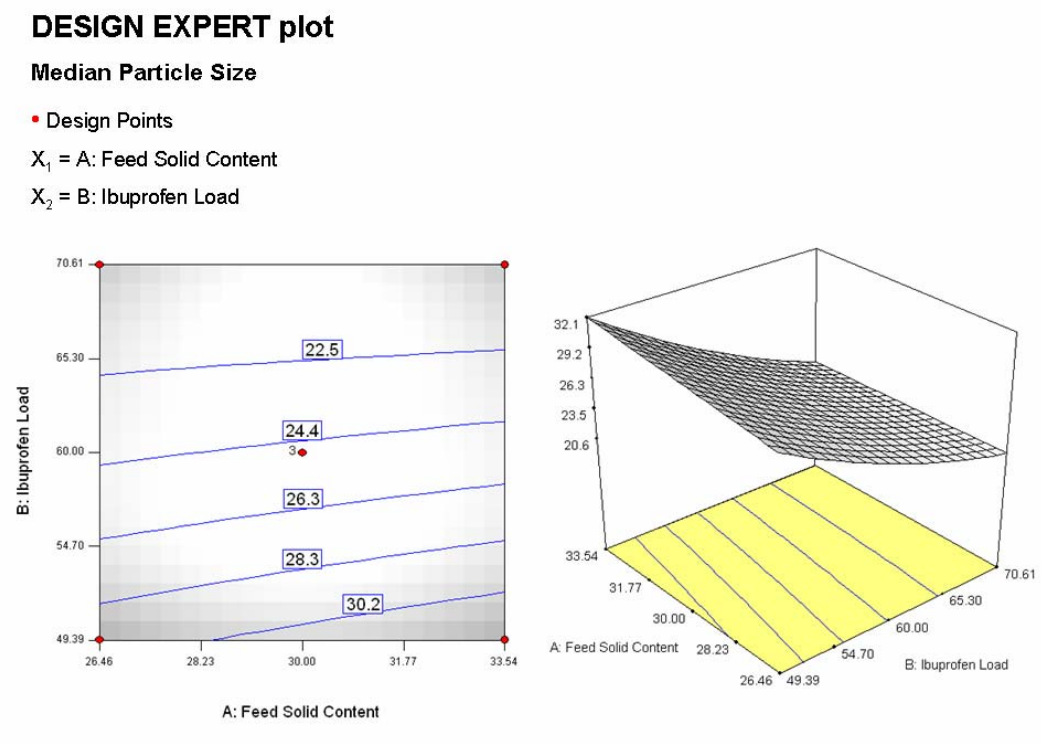

Fig. 5. Influence of solid content of the feed suspension and ibuprofen concentration on median particle size

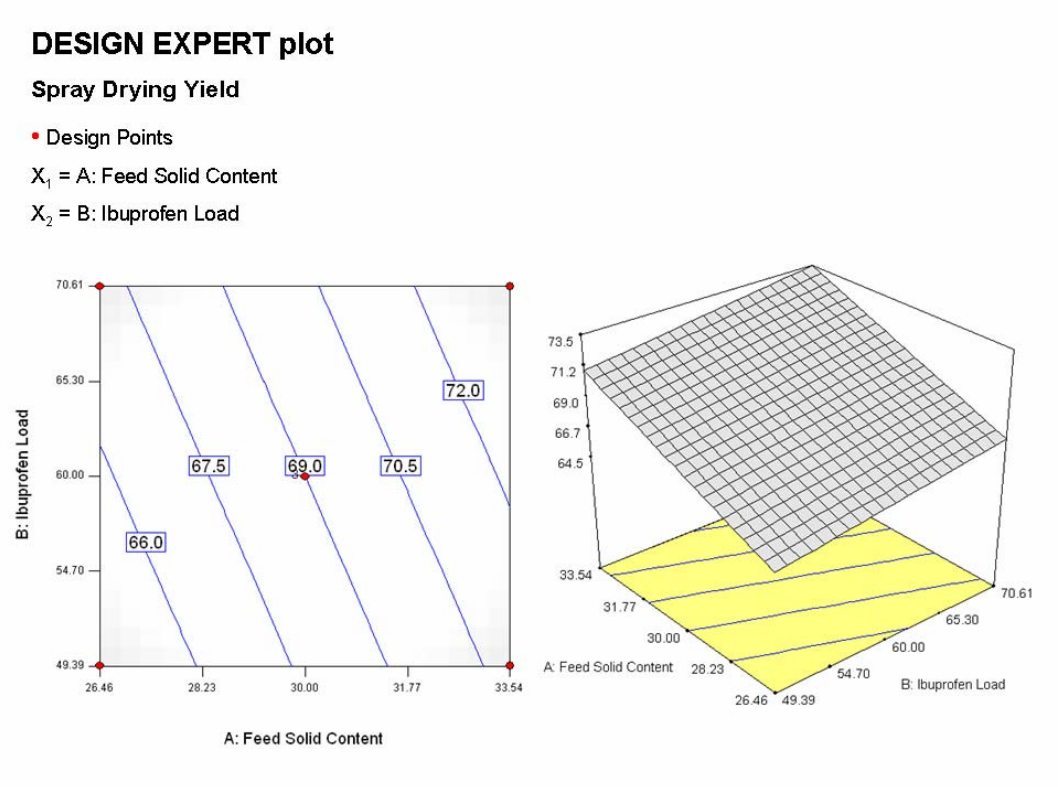

Fig. 6. Influence of solid content of the feed suspension and ibuprofen concentration on process yield

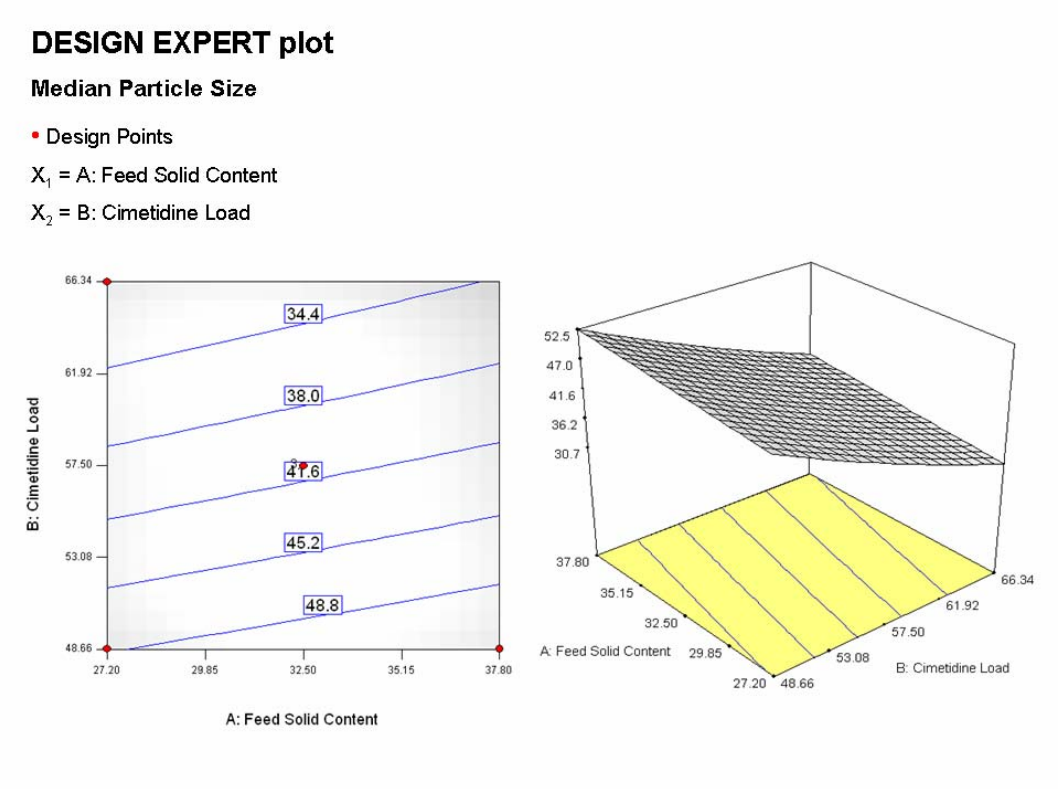

Fig. 7. Influence of solid content of the feed suspension and cimetidine concentration on median particle size

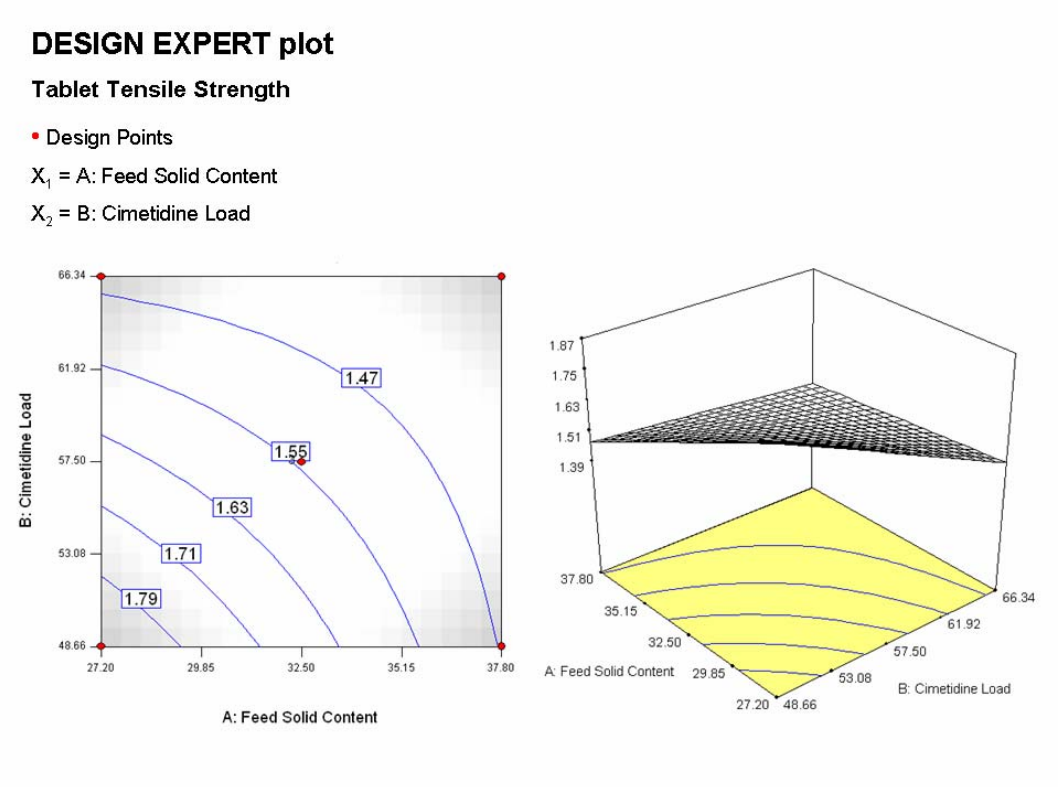

Fig. 8. Influence of solid content of the feed suspension and cimetidine concentration on tablet tensile strength

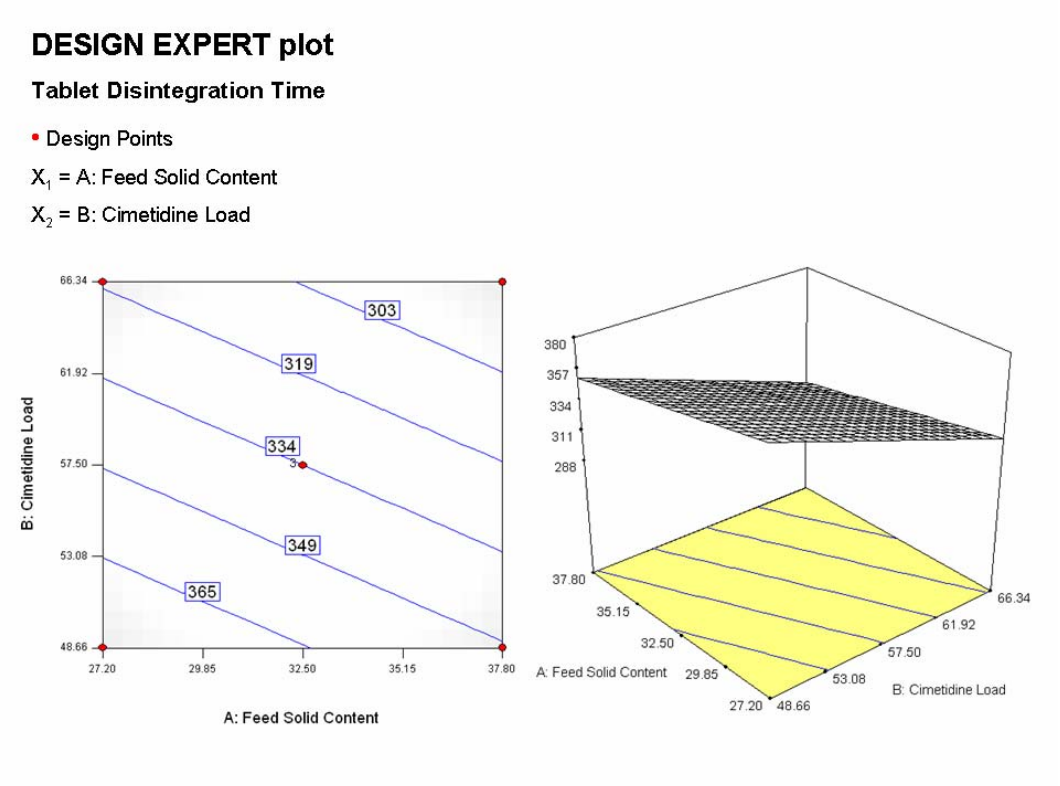

Fig. 9. Influence of solid content of the feed suspension and cimetidine concentration on tablet disintegration time

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 14). At higher acetaminophen 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. run 10, 8 and 5 at a solid concentration of 25.0, 32.5 and 40.0% w/w, respectively). Similarly, Chapter 4 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 16), 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 17, while the corresponding contour plots are given in Fig. 10–16.

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 run 6, 11)(Table 8, 14), 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 [7]), 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 9, 15). 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 8). 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 9).

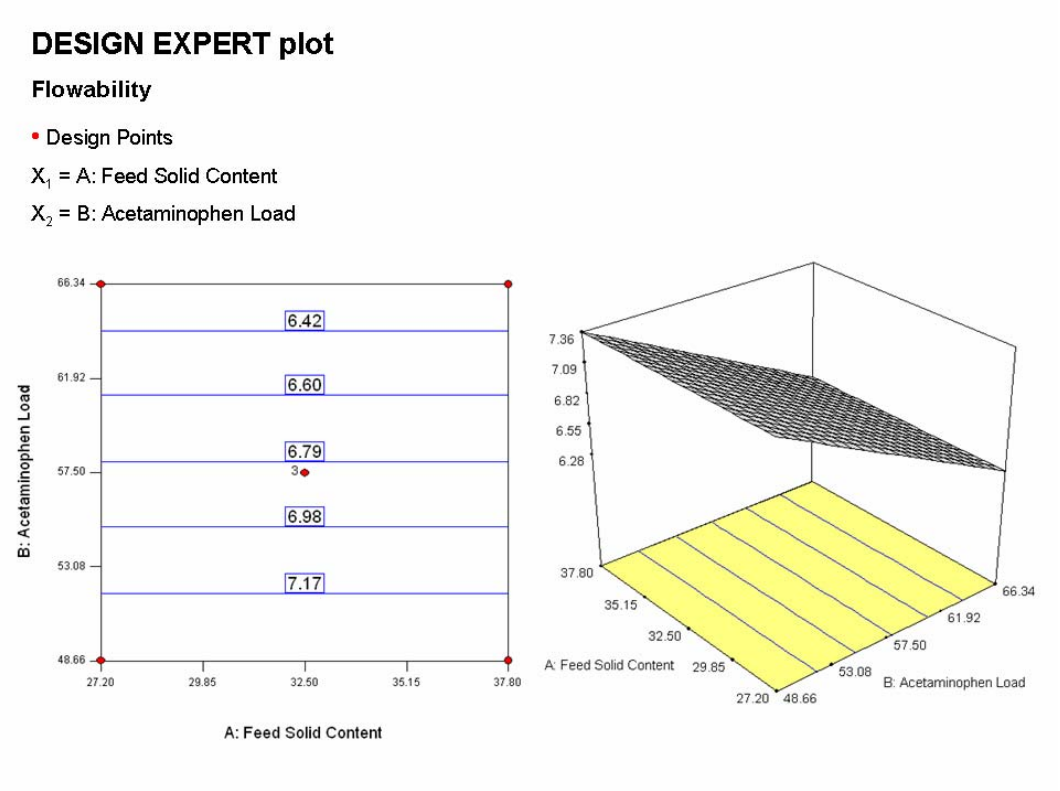

Fig. 10. Influence of acetaminophen concentration on flowability

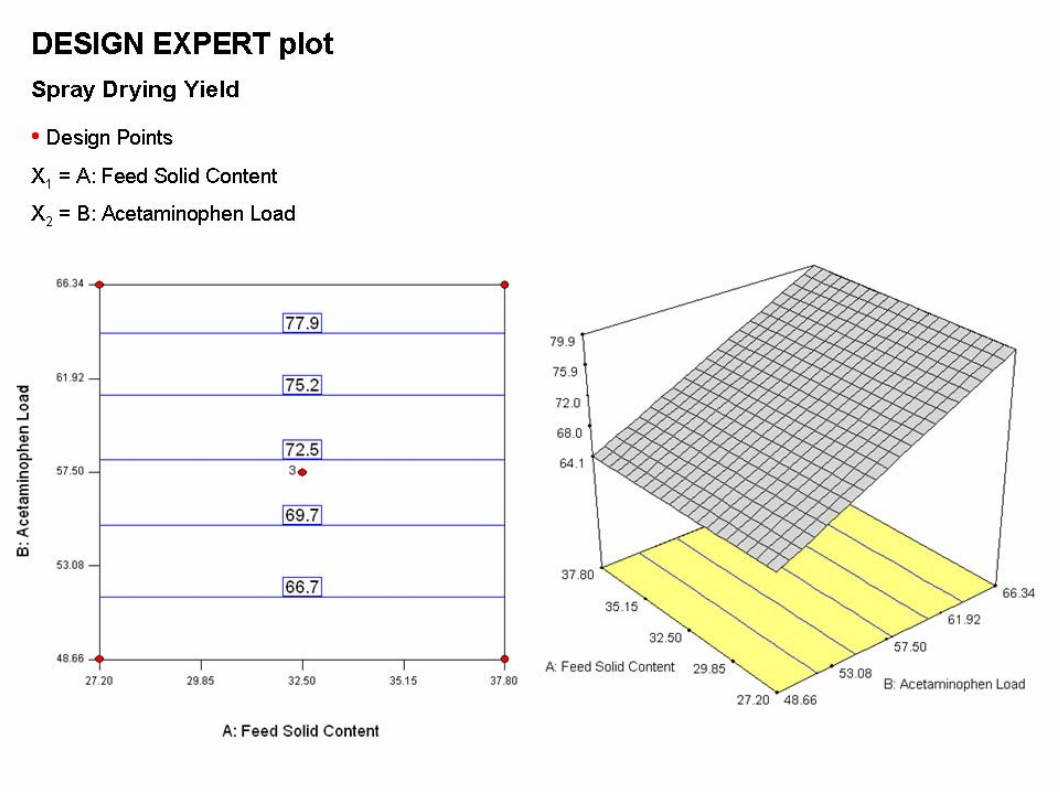

Fig. 11. Influence of acetaminophen concentration on process yield

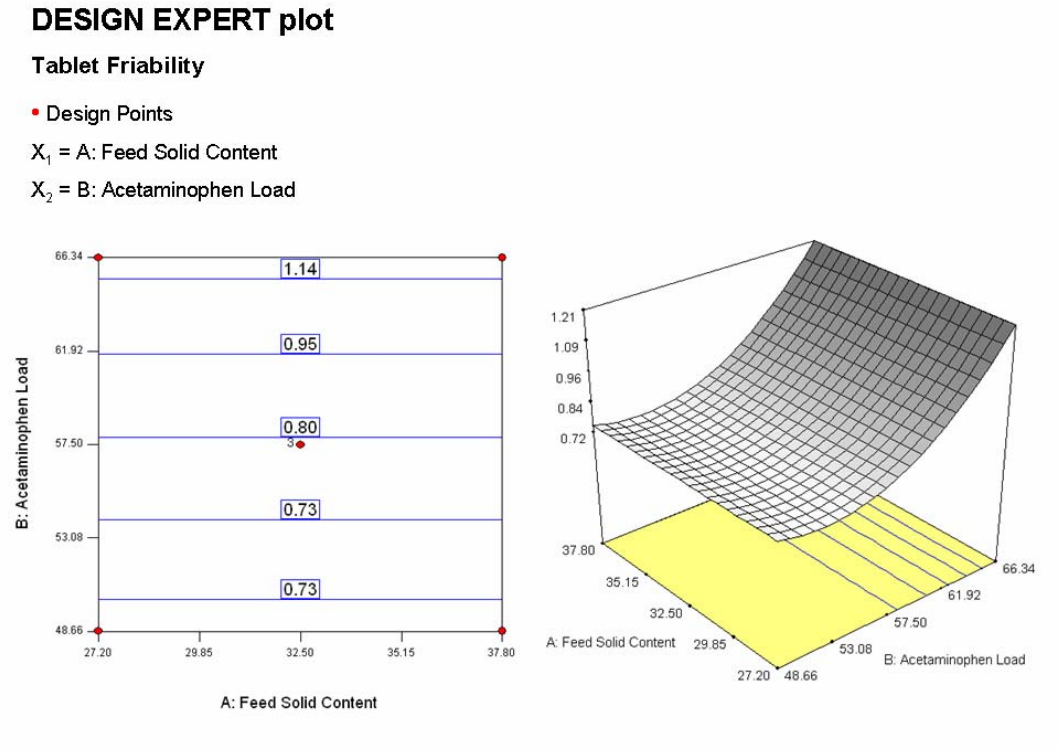

Fig. 12. Influence of acetaminophen concentration on tablet friability

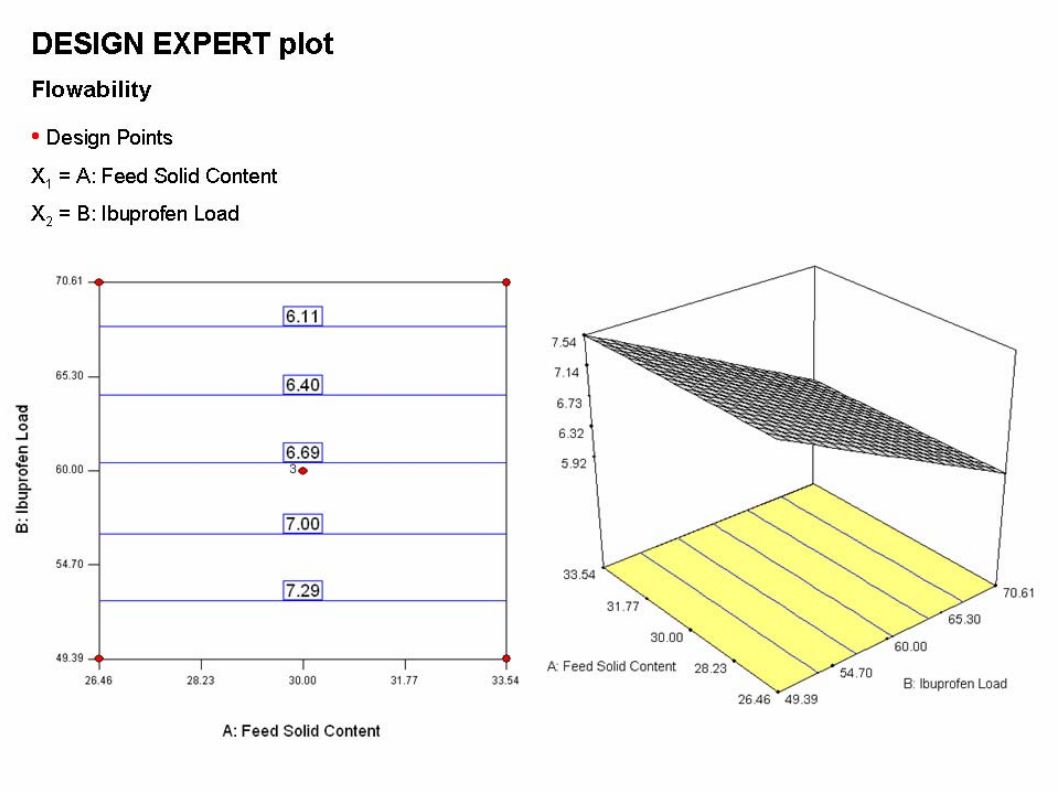

Fig. 13. Influence of ibuprofen concentration on flowability

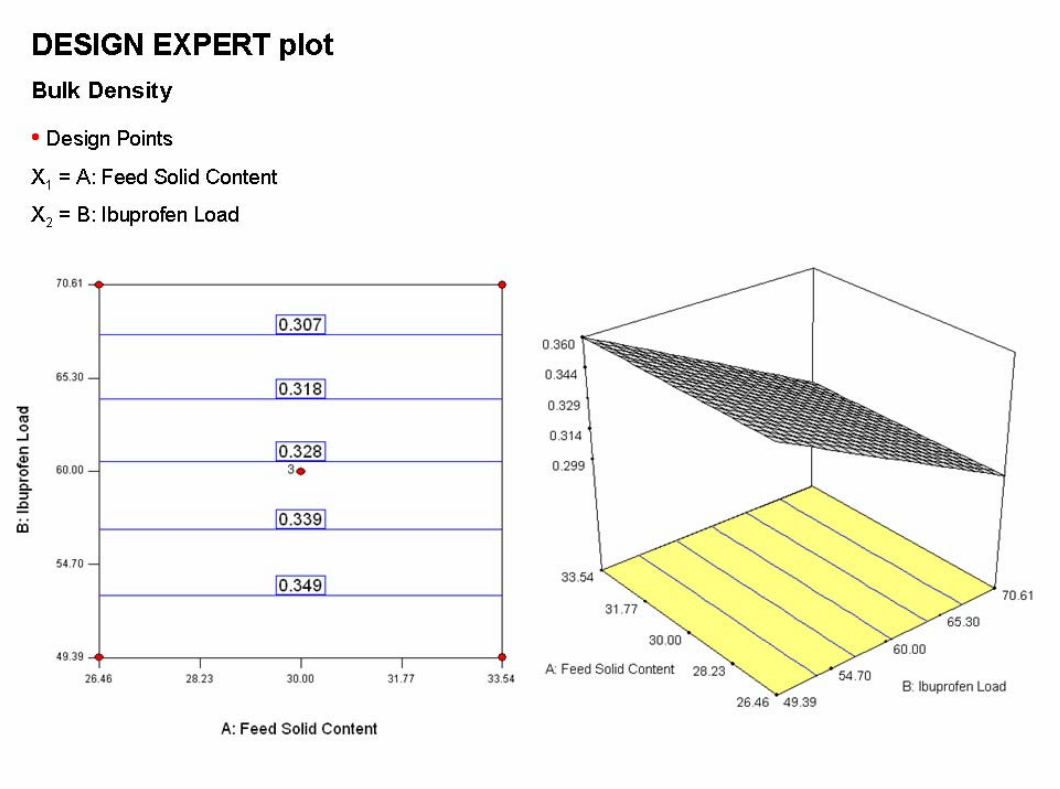

Fig. 14. Influence of ibuprofen concentration on density

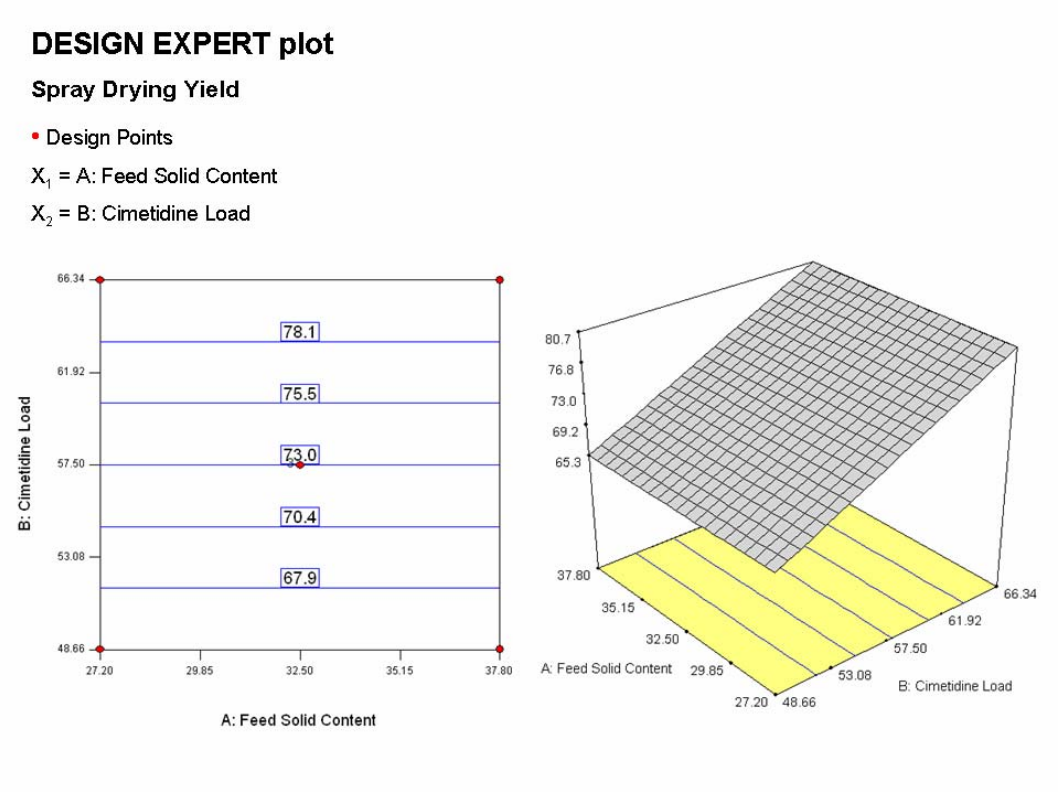

Fig. 15. Influence of cimetidine concentration on process yield

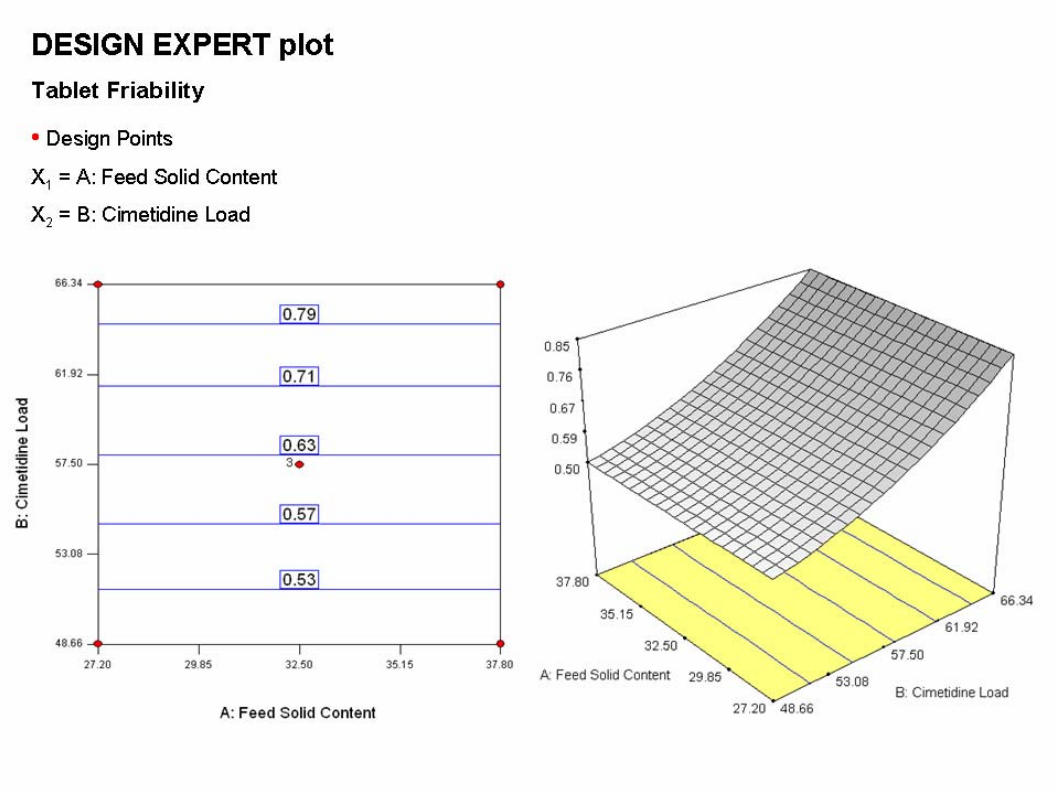

Fig. 16. Influence of cimetidine concentration on tablet friability

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 17) 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: 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^{TM} 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 7). Tablet tensile strength, disintegration time and friability were within acceptable ranges: 1.08 ± 0.14 MPa, 269 ± 58 s, 0.85 ± 0.12 %, respectively (Table 7).

3.2.2 Scaling-up of ibuprofen formulation

Similarly to acetaminophen, numerical optimisation was performed using statistical models (Table 17) 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: 15000–20000 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°C and 66–65°C resulted in smaller spray dried particles (median particle size: ± 100 µm). A reduction of the rotary atomiser speed to 15000 rpm (experiment 5) increased the median particle size (120 µm). Nevertheless, spray dried powders produced using process parameters in test 3, 4 and 5 showed poor powder flowability.

During tablet production on a rotary Modul^{TM} 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 7. Tablet tensile strength, disintegration time and friability were within acceptable ranges: 0.92 ± 0.03 MPa, 376 ± 31 s, 0.82 ± 0.08 %, respectively (Table 7).

3.3 Physico-chemical properties of the optimised formulations

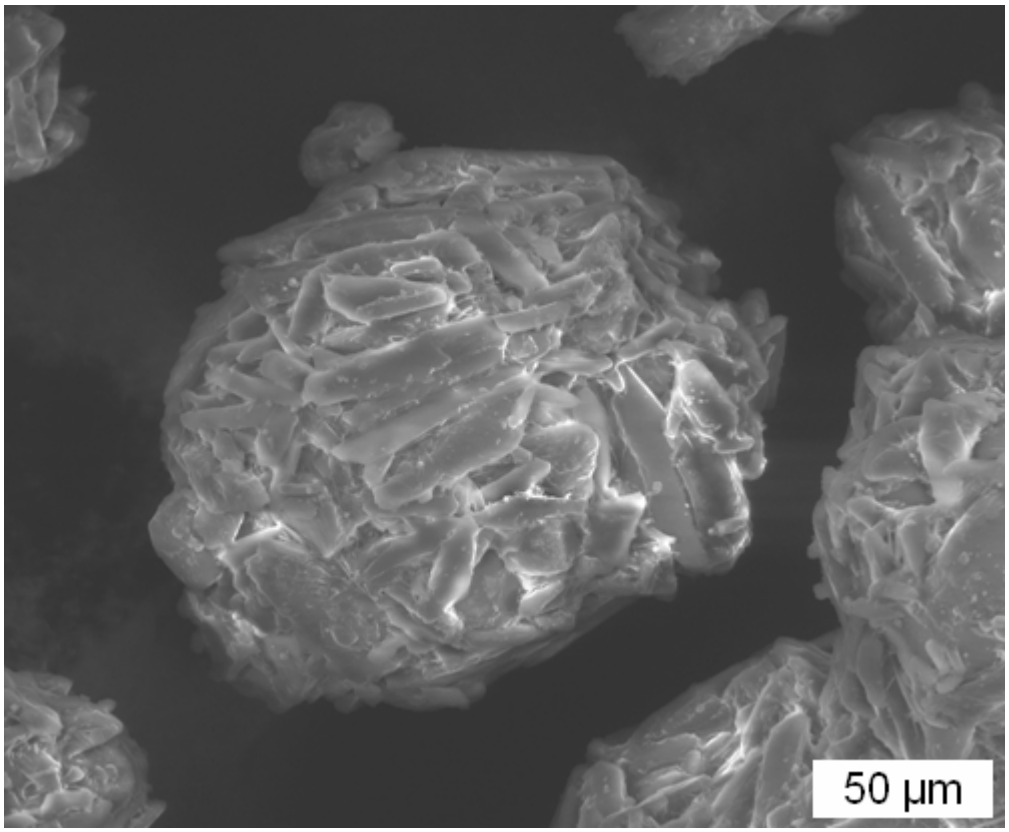

Fig. 17. SEM picture of acetaminophen formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 70% w/w)

SEM pictures of the powder mixtures containing acetaminophen (Fig. 17) and ibuprofen (Fig. 18) processed on a production-scale spray dryer using optimal process conditions showed spherical agglomerates containing acetaminophen, while the ibuprofen formulation resulted in irregular agglomerates.

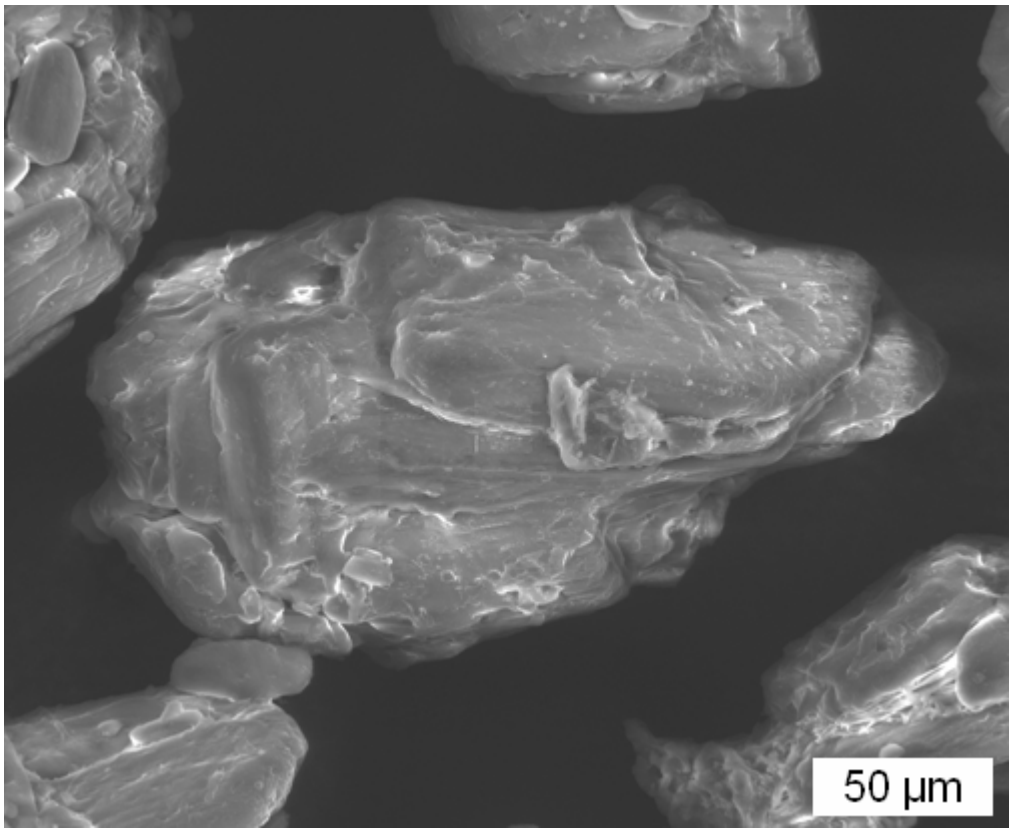

Fig. 18. SEM picture of ibuprofen formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 75% w/w)

After lab-scale production of powder mixtures containing cimetidine, SEM pictures (Fig. 19) 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.

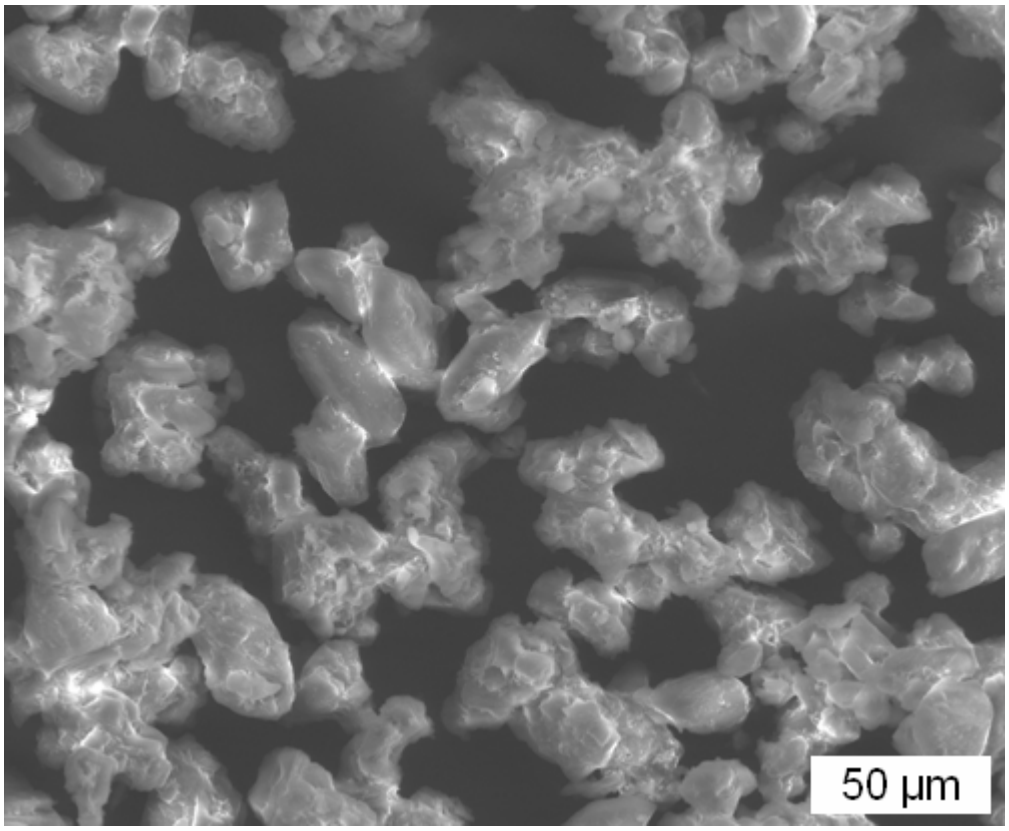

Fig. 19. SEM picture of cimetidine formulation (total solid content of the feed suspension: 35% w/w, drug concentration: 70% w/w)

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

In addition, Fig. 20 showed the X-ray diffraction spectra of 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.

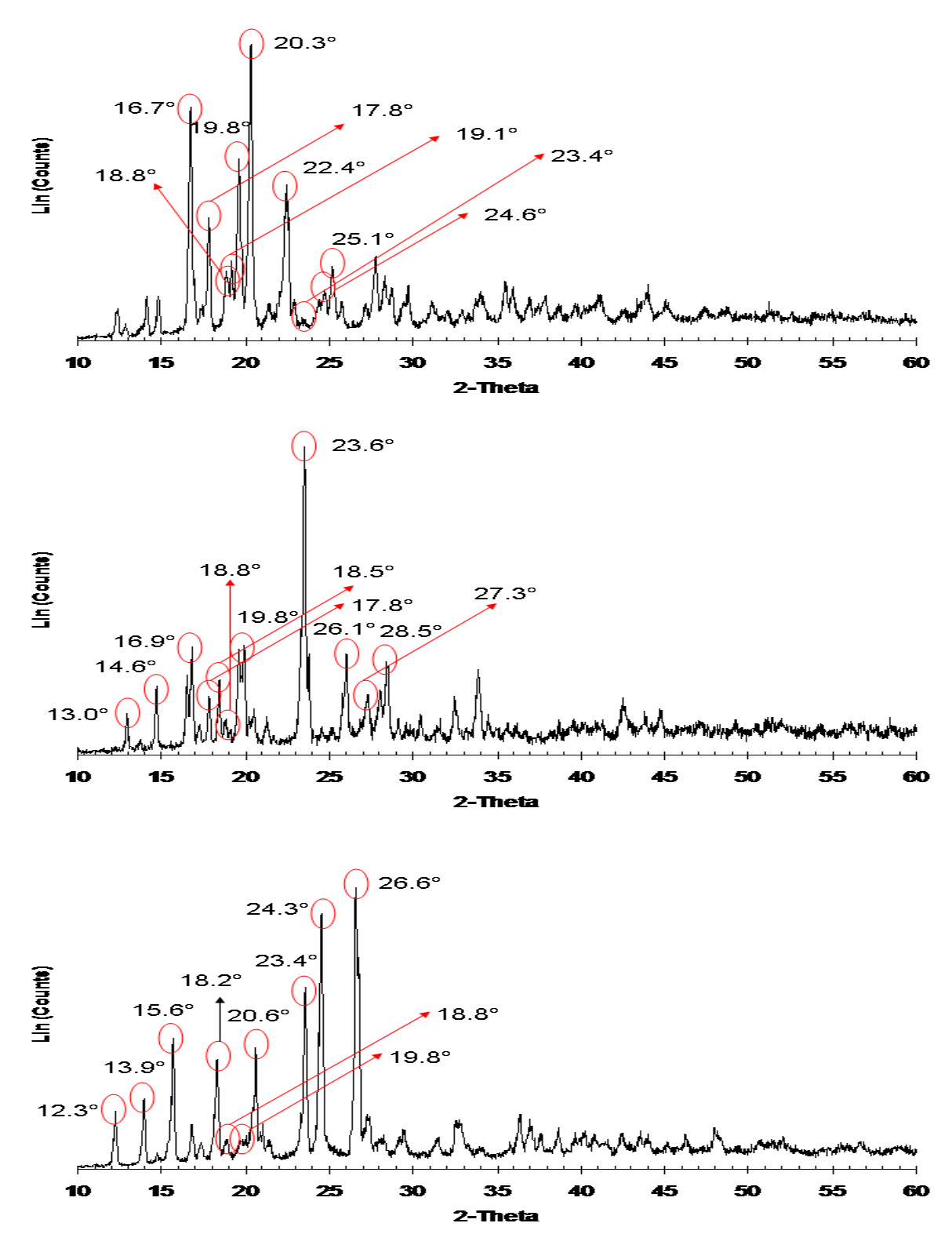

Fig. 20. X-ray diffraction pattern of optimal acetaminophen (top), ibuprofen (middle) and cimetidine (bottom) formulation

Dissolution results (Fig. 21) 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. In Chapter 3 loss of superdisintegrant during coprocessing was reported 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 ± 0.04 % w/w and 6.07 ± 0.07 % w/w for acetaminophen and ibuprofen formulations, respectively (theoretical disintegrant concentration: 6.0% w/w). The dissolution profiles of acetaminophen- and ibuprofen-containing tablets complied with the requirements of the U.S. Pharmacopoeia, i.e. more than 80% acetaminophen and ibuprofen released after 30 and 60 min, respectively. Dissolution profiles of the optimised cimetidine formulation produced on a lab-scale spray dryer showed a complete release within 15 min.

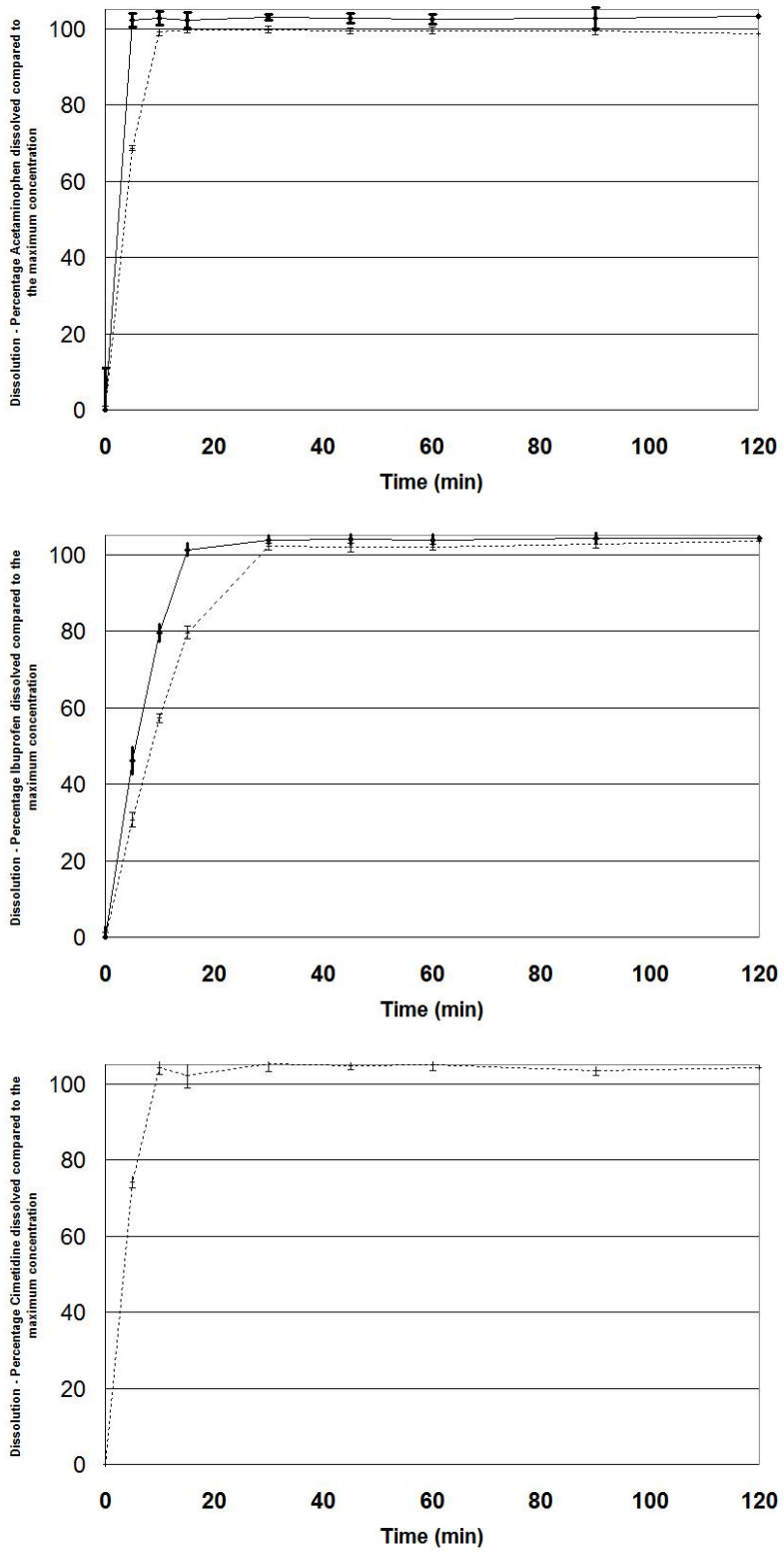

Fig. 21. Dissolution of acetaminophen- (top), ibuprofen- (middle) and cimetidine- (bottom) containing tablets produced on a lab scale (……) and production scale (_____) spray dryer.

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 compaction, resulting in a fully continuous manufacturing process.

5 Acknowledgements

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CONCLUSIONS AND SUMMARY

CONCLUSIONS AND SUMMARY

Coprocessing via spray drying was developed as an alternative manufacturing technique to improve the compactability of highly dosed and poorly compressible drug substances. In contrast to (wet) granulation techniques, this production process is fully continuous and requires no intermediate milling or blending steps in between particle formation and compression. Coprocessing via spray drying of drug substance, carbohydrates (erythritol, maltodextrin, mannitol), superdisintegrant (crospovidone), glidant (colloidal silicon dioxide) and surfactant (polyoxyethylene 20 sorbitan monooleate) was feasible to improve the processibility, hygroscopicity, flowability and compactability of powders in comparison with physical mixtures of the different components.

Using the newly developed coprocessing technique the number of process steps is reduced, production efficiency is improved and costs are cut to increase profit. In addition, continuous manufacturing reduces the time-to-market (scale-up benefits, better quality), capital investment, labour costs, floor space and wastage. These features of coprocessing via spray drying offer many obvious economic benefits for a pharmaceutical production facility.

Some drawbacks of the newly developed manufacturing technique are:

- the developed formulation platform consisted of a two-step process (co-spray drying and compaction) for acetaminophen and ibuprofen formulations, but in the case of cimetidine an additional blending step with magnesium stearate needed to be incorporated in order to avoid lubrication problems during compaction.
- no relationship between the physico-chemical properties of the tested drug substances and the properties of the spray dried particles has been established. Although such a correlation would increase the value of this manufacturing platform, the number of drug substances tested so far is too limited and this work must be extended before such a relationship can be defined.

CHAPTER 1 described a detailed screening of the coprocessing of acetaminophen with a wide range of water soluble filler/binders (erythritol, isomalt, lactitol, lactose, maltitol, maltodextrin, mannitol, sorbitol and xylitol). Coprocessing via spray drying was performed to prepare binary and ternary powder mixtures containing acetaminophen and carbohydrates in order to improve the drug compactability. Acetaminophen was used as model drug because of

its poor compactability, capping and lamination problems. Evaluation was based on processibility, powder hygroscopicity, flowability, compactability and Heckel analysis. Erythritol, maltodextrin and mannitol yielded non-sticky powders after co-spray drying with acetaminophen in combination with excellent process yields, whereas coprocessing of acetaminophen with isomalt, lactitol, maltitol, sorbitol and xylitol resulted in several process problems: vitrification (sorbitol), blocking of pipings and cyclone (isomalt), low process yields due to their gummy-like and thermoplastic nature (lactitol, maltitol, xylitol). Maltodextrin and mannitol improved compactability, while erythritol increased powder flowability and density. Thus, a combination of erythritol, maltodextrin and mannitol was selected for further formulation optimisation and process development.

CHAPTER 2 reported the use of experimental design to optimise the ratio of the selected excipients (erythritol, maltodextrin, mannitol) in a 4-component powder mixture (containing acetaminophen) produced via co-spray drying. Evaluation was based on spray drying process yield, residual moisture content, powder flowability, density, hygroscopicity, median particle size and compactability. Significant models were constructed for powder flowability, median particle size, density, hygroscopicity, tablet tensile strength, friability and disintegration time. Changes in maltodextrin content strongly influenced median particle size, density, hygroscopicity and tablet properties, while the erythritol and mannitol concentration had less influence on the physico-chemical properties of the spray dried powder mixtures and tablets. Consequently, an optimised formulation was selected for further development and process optimisation. A combination of mannitol, erythritol and maltodextrin was suitable to improve the tablet properties of acetaminophen. Numerical optimisation was applied to determine the optimal contents of mannitol (11.6% w/w), erythritol (20.9% w/w) and maltodextrin (13.9% w/w).

In **CHAPTER 3** different maltodextrin grades were studied with special focus on the influence of amylose/amylopectin ratio on tablet properties. In addition, the effect of superdisintegrant type and grade (croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate (Explotab®), crospovidone (Kollidon® CL, Kollidon® CL-M, Polyplasdone® XL, Polyplasdone® XL-10) on powder and tablet properties was investigated. The amylose/amylopectin ratio had a strong influence on the tablet tensile strength, disintegration time and friability. Tablet tensile strength and friability of formulations containing Glucidex® 2 (1–5% amylose) and 9 (20% amylose) were similar. However, the high amylose

maltodextrin (Unipure DC, 50–70 amylose) lowered tablet tensile strength, whereas friability was increased. The higher the amylose/amylopectin ratio, the lower the tablet disintegration time. Thus, Glucidex® 9 was selected as optimal maltodextrin grade because of improved tablet disintegration time compared to Glucidex® 2 and lower tablet friability in comparison with Unipure DC. Co-spray drying of acetaminophen, carbohydrates and a superdisintegrant in a lab-scale spray dryer yielded powders with a significant loss of superdisintegrant due to preferential deposition of the disintegrant on the wall of drying chamber during processing. Croscarmellose sodium and sodium starch glycolate were less effective for tablet disintegration than crospovidone, probably their swelling formed a gel which blocked tablet pores and prevented further penetration of water into the inner layers of the tablet. Crospovidone did not form a gel which retarded disintegration and dissolution. Kollidon® CL minimised tablet disintegration time in comparison with other crospovidone grades because of its excellent wicking and swelling properties due to its larger particle size and high porosity.

In **CHAPTER 4** the optimisation of the co-spray drying process was described. A combination of acetaminophen, mannitol, erythritol, maltodextrin (Glucidex® 9), crospovidone (Kollidon® CL), colloidal silicon dioxide and polyoxyethylene 20 sorbitan monooleate was selected for process optimisation (solid content of the feed suspension, atomisation pressure, inlet and outlet drying air temperature) of 'ready-to-compress' co-spray dried powders intended for direct compression. Colloidal silicon dioxide was used as yield-increasing agent, while polyoxyethylene 20 sorbitan monooleate was included to improve the quality of the feed suspension used for co-spray drying in case of highly dosed poorly water soluble drug substance (preventing agglomeration of suspended particles and sticking to the container surface) and to decrease tablet disintegration time. Significant models were constructed for powder flowability, median particle size, density, residual moisture content and spray drying process yield. Atomisation pressure only influenced the powder flowability, while tablet tensile strength, disintegration time and friability were robust and independent of the process conditions. An optimised spray drying process with an atomisation pressure of 6 bar and an inlet and outlet drying air temperature of 221 and 81°C, respectively, was selected for further scale-up trials.

CHAPTER 5 evaluated if coprocessing via spray drying could be used as a formulation platform to improve the compactability of various drugs. Formulations containing acetaminophen, ibuprofen and cimetidine were produced on a lab-scale spray dryer, while the

optimised acetaminophen and ibuprofen formulations were scaled-up on a production-scale spray dryer. In addition, drug concentration and solid content of the feed suspension were optimised. These highly dosed acetaminophen (drug load: 70% w/w), ibuprofen (drug load: 75% w/w) and cimetidine (drug load: 70% w/w) directly compressible powders were produced by co-spray drying aqueous suspensions with a solid content of 35% w/w and the resulting powders were directly compressed. Scaling-up of optimised acetaminophen and ibuprofen formulations on a production-scale spray dryer and rotary tablet press was performed, resulting in a fully continuous manufacturing process. During tablet production on a rotary Modul^{TM} P tablet press, tablet tensile strength, disintegration time and friability of acetaminophen and ibuprofen formulations were within acceptable ranges.

Based on the work performed during this project a number of topics can be identified for future research dealing with coprocessing via spray drying and the improvement of drug compactability:

- although a fully continuous manufacturing process without intermediate milling or blending steps was developed for acetaminophen and ibuprofen formulations (Chapter 5), process problems due to insufficient lubrication can occur when incorporating other drug substances. A future challenge is to immediately incorporate a lubricant during coprocessing of drug and excipients, effectively improving the lubrication of the directly compressible coprocessed powder mixtures without an additional blending step. During preliminary work we already incorporated a lubricant (Mg-stearate) in the feed suspension. However, the amount of magnesium stearate at the surface of the spray dried particles was insufficient to have efficient lubrication. This problem can possibly be overcome by adding the lubricant to the system after the spray dried particles have been formed (e.g. by continuously nebulisation of magnesium stearate powder in the piping before the cyclone or in a horizontal fluid-bed dryer connected to the cyclone), thus coating the particles with a layer of lubricant particles.
- besides the use of polyols and maltodextrin, excipients such as starch, (silicified) microcrystalline cellulose, dicalcium phosphate, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, ethylcellulose, polyvinylpyrrolidone and its copolymers and polyethylene glycol could be evaluated on their ability to improve the compactability of drugs via coprocessing.

- the development of a similar formulation platform for poorly water soluble drug substances based on organic solutions/suspensions in order to prepare ‘ready-to-compress’ solid dispersions and to improve drug dissolution and bioavailability.

CONCLUSIES EN SAMENVATTING

CONCLUSIES EN SAMENVATTING

'Coprocessing' door middel van sproeidrogen werd ontwikkeld als een alternatieve productietechniek om de compacteerbaarheid van hoog gedoseerde en slecht comprimeerbare geneesmiddelen te verhogen. In tegenstelling tot (natte) granulatietechnieken is een dergelijk productieproces volledig continu. Er zijn geen additionele maal- of mengstappen vereist tussen deeltjesvorming en compressie. Door middel van cosproeidrogen van een geneesmiddel met koolhydraten (erythritol, maltodextrine, mannitol), superdesintegrant (crospovidone), glijmiddel (colloïdaal silicium dioxide) en surfactant (polyoxyethyleen 20 sorbitan monooleaat) verbeterde de produceerbaarheid, hygroscopiciteit, vloeibaarheid en compacteerbaarheid van de geproduceerde poeders voor directe compressie in vergelijking met de individuele componenten.

Door gebruik te maken van de nieuw ontwikkelde productietechniek werd het aantal processtappen gereduceerd en de productie-efficiëntie verbeterd. Tevens worden de productiekosten verminderd zodat de winst verhoogt. Daarenboven reduceert continue productie de 'time-to-market' (voordelen bij opschalen, betere kwaliteit), kapitaalinvesteringen, werkingskosten, vereist oppervlak en productverlies. Deze kenmerken van 'coprocessing' via sproeidrogen leveren talrijke duidelijke economische voordelen op voor een farmaceutische productiefaciliteit.

Enkele gebreken van de nieuw ontwikkelde productietechniek zijn:

- het ontwikkeld formulatieplatform bestaat uit een 2-staps proces (cosproeidrogen en compactie) voor acetaminophen- en ibuprofen-formulaties, maar in het geval van cimetidine is een bijkomende mengstap met magnesium stearaat vereist om smeringsproblemen tijdens compactie te voorkomen.
- er kon geen relatie vastgesteld worden tussen de fysico-chemische eigenschappen van de geteste geneesmiddelen en de eigenschappen van de gesproeidroogde deeltjes. Alhoewel een dergelijke correlatie de waarde van dit productieplatform zou verhogen, is het aantal geteste geneesmiddelen te beperkt en zou dit werk moeten uitgebreid worden om een dergelijk relatie te definiëren.

HOOFDSTUK 1 beschreef een gedetailleerd onderzoek betreffende 'coprocessing' van acetaminophen met water oplosbare vul- en/of bindmiddelen (erythritol, isomalt, lactitol,

lactose, maltitol, maltodextrine, mannitol, sorbitol and xylitol). Binaire en ternaire poedermengsels van acetaminophen en koolhydraten werden bereid door middel van 'coprocessing' via sproeidrogen met als doel de compacteerbaarheid van het geneesmiddel te verbeteren. Acetaminophen werd gekozen als modelgeneesmiddel omwille van zijn beperkte compacteerbaarheid, 'capping' en 'laminatie' problemen. De produceerbaarheid, hygroscopiciteit, vloeibaarheid, compacteerbaarheid werden geëvalueerd. Erythritol, maltodextrine en mannitol resulteerden in niet-kleverige poeders na cosproeidrogen met acetaminophen in combinatie met uitstekende procesopbrengsten. 'Coprocessing' van acetaminophen met isomalt, lactitol, maltitol, sorbitol and xylitol bracht verscheidene procesproblemen met zich mee: vitrificatie (sorbitol), blokkeren van buizen en cycloon (isomalt), lage procesopbrengsten vanwege hun gomachtige en thermoplastische aard (lactitol, maltitol, xylitol). Maltodextrine en mannitol verbeterde de compacteerbaarheid, terwijl erythritol de vloeibaarheid en densiteit verhoogde. Bijgevolg werd een combinatie van erythritol, maltodextrine en mannitol geselecteerd voor bijkomende formulatie-optimalisatie en procesontwikkeling.

HOOFSTUK 2 vermeldde het gebruik van 'experimental design' om de verhouding van de geselecteerde excipiënten (erythritol, maltodextrin, mannitol) in een 4-componenten poedermengsel (bevattende acetaminophen) te optimaliseren. De procesopbrengst, vochtgehalte, vloeibaarheid, densiteit, hygroscopiciteit, gemiddelde deeltjesgrootte en compacteerbaarheid werden geëvalueerd. Significante modellen voor vloeibaarheid, gemiddelde deeltjesgrootte, densiteit, hygroscopiciteit, tabletsterkte, -friabiliteit en -desintegratietijd werden opgebouwd. Concentratieveranderingen van maltodextrine beïnvloedden sterk de gemiddelde deeltjesgrootte, densiteit, hygroscopiciteit en tableteigenschappen, terwijl de concentratie van erythritol en mannitol minder invloed had op de fysico-chemische eigenschappen van de gesproeidroogde poedermengsels en tabletten. Bijgevolg werd een optimale formulatie geselecteerd voor verdere ontwikkeling en procesoptimalisatie. Een combinatie van mannitol, erythritol en maltodextrine was geschikt om de tableteigenschappen van acetaminophen te verbeteren. Numerieke optimalisatie werd aangewend om de optimale gehaltes aan mannitol (11.6% w/w), erythritol (20.9% w/w) en maltodextrine (13.9% w/w) te bepalen.

In **HOOFDSTUK 3** werden 3 verschillende maltodextrine types bestudeerd met speciale aandacht voor de invloed van de amylose/amylopectine verhouding op de

tableteigenschappen. Daarenboven werd het effect van de klasse en het type superdesintegrant (vernet carboxymethylcellulose (Ac-Di-Sol®), vernet carboxymethylzetmeel (Explotab®), vernet polyvinylpyrrolidone (Kollidon® CL, Kollidon® CL-M, Polyplasdone® XL, Polyplasdone® XL-10)) op de poeder- en tableteigenschappen onderzocht. De amylose/amylopectine verhouding had een sterke invloed op de tabletsterkte, -desintegratietijd en -friabiliteit. De tabletsterkte en -friabiliteit van formulaties met Glucidex® 2 (1–5% amylose) en 9 (20% amylose) waren vergelijkbaar. De maltodextrine met een hoog amylose gehalte (Unipure DC, 50–70 amylose) verlaagde de tabletsterkte, terwijl de tablet friabiliteit werd verhoogd. Hoe hoger de amylose/amylopectine verhouding, des te lager de tabletdesintegratietijd. Bijgevolg werd Glucidex® 9 geselecteerd als optimaal maltodextrine type omwille van een verbetering van de desintegratietijd in vergelijking met Glucidex® 2 en een lagere tabletfriabiliteit in vergelijking met Unipure DC. Cosproeidrogen van acetaminophen, koolhydraten en een superdesintegrant in een laboschaal sproeidroger resulteerde in poeders met een significant verlies aan superdesintegrant omwille van preferentiële afzetting van desintegrant op de wanden van de droogkamer tijdens productie. Vernet carboxymethylcellulose en vernet carboxymethylzetmeel waren minder effectief in tabletdesintegratie dan vernet polyvinylpyrrolidone. Vermoedelijk vormde hun zwelling een gel, welke de tabletporiën blokkeerde, en alzo een verdere penetratie van water voorkwam in diepere tabletlagen. Vernet polyvinylpyrrolidone vormde geen gel waardoor het desintegreren en oplossen vertraagde. Kollidon® CL minimaliseerde de tabletdesintegratie in vergelijking met andere polyvinylpyrrolidone types omwille van zijn uitstekende ‘wicking’ en zwellingseigenschappen vanwege zijn grotere deeltjesgrootte en hoge porositeit.

In **HOOFDSTUK 4** werd de optimalisatie van het sproeidroogproces beschreven. Een combinatie van acetaminophen, mannitol, erythritol, maltodextrine (Glucidex® 9), vernet polyvinylpyrrolidone (Kollidon® CL), colloïdale silicium dioxide en polyoxyethyleen 20 sorbitan monooleaat werd geselecteerd voor procesoptimalisatie (vaste stof concentratie van de suspensie, atomisatiedruk, inlaat- en uitlaattemperatuur van de drogende lucht) van ‘ready-to-compress’ gecosproeidroogde poeders. Colloïdale silicium dioxide werd gebruikt om de procesopbrengst te verhogen. Polyoxyethyleen 20 sorbitan monooleaat werd toegevoegd om de kwaliteit van de suspensie te verbeteren in geval van hoog gedoseerde en beperkt wateroplosbare geneesmiddelen en om de tabletdesintegratie te verlagen. Significante modellen voor vloeibaarheid, gemiddelde deeltjesgrootte, densiteit, vochtgehalte en procesopbrengst werden opgesteld. De atomisatiedruk beïnvloedde enkel de vloeibaarheid

van de poeders, terwijl tabletsterkte, -desintegratietijd en -friabiliteit robuust waren, onafhankelijk van de procescondities. Een geoptimaliseerd sproeidroogproces met een atomisatiedruk van 6 bar en een inlaat- en uitlaattemperatuur van respectievelijk 221 en 81°C, werd geselecteerd voor verdere opschalingsexperimenten.

In **HOOFDSTUK 5** werd nagegaan of 'coprocessing' via sproeidrogen kon gebruikt worden als een formulatieplatform om de compacteerbaarheid van talrijke geneesmiddelen te verbeteren. Acetaminophen-, ibuprofen- en cimetidine-formulaties werden geproduceerd in een laboschaal sproeidroger, terwijl de geoptimaliseerde acetaminophen- en ibuprofen-formulaties werden opgeschaald in een productie-sproeidroger. Daarenboven werden de concentratie van het geneesmiddel en de vaste stof concentratie van de suspensie geoptimaliseerd. Deze direct comprimeerbare en hoog gedoseerde acetaminophen (geneesmiddelconcentratie: 70% w/w), ibuprofen (geneesmiddelconcentratie: 75% w/w) en cimetidine (geneesmiddelconcentratie: 70% w/w) poeders werden geproduceerd door middel van cosproeidrogen van waterige suspensies met een vaste stof concentratie van 35% w/w. Deze poeders waren direct comprimeerbaar. Het opschalen van de geoptimaliseerde acetaminophen- en ibuprofen-formulaties op een productieschaal sproeidroger en rotatieve tabletpers werd uitgevoerd met als resultaat een volledig continu productieproces. Tijdens tabletproductie op een rotatieve Modul^{TM} P pers waren de tabletsterkte, -desintegratietijd en -friabiliteit van de acetaminophen- en ibuprofen-formulaties binnen aanvaardbare grenzen.

Op basis van het uitgevoerde werk tijdens dit project kunnen verscheidene onderwerpen voor toekomstig onderzoek geïdentificeerd worden:

- alhoewel een volledig continu productieproces zonder additionele maal- of mengstappen ontwikkeld werd voor acetaminophen- en ibuprofen-formulaties (Hoofdstuk 5), kunnen procesproblemen voorkomen bij andere geneesmiddelen vanwege onvoldoende smering. Een toekomstige uitdaging is een directe opname van een smeermiddel tijdens 'coprocessing' van een geneesmiddel met excipiënten, waardoor de smering van direct comprimeerbare en gecoproduceerde poedermengsels effectief verbetert zonder bijkomstige mengstap. Tijdens voorafgaand onderzoek hebben we reeds een smeermiddel (Mg-stearaat) toegevoegd aan de suspensie. De hoeveelheid aan magnesium stearaat op het oppervlak van de gesproeidroogde deeltjes was echter onvoldoende voor een efficiënte smering. Dit probleem kan eventueel verholpen worden door een smeermiddel toe te voegen aan het systeem nadat de

gesproeidroogde deeltjes gevormd zijn (vb. door middel van continue poederverstuiving van magnesium stearaat in het buissysteem voor de cycloon of in een horizontale wervelbeddroger die verbonden is achter de cycloon), waardoor de deze gecoat worden met smeermiddeldeeltjes.

- Naast het gebruik van polyolen en maltodextrine kunnen excipiënten zoals (gesilifieerde) microkristallijne cellulose, dicalciumfosfaat, hydroxypropylmethyl-cellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, ethyl-cellulose, polyvinylpyrrolidone (en zijn copolymeren) en polyethyleen glycol geëvalueerd worden op hun vermogen om de compacteerbaarheid van geneesmiddelen te verbeteren door middel van 'coprocessing'.
- De ontwikkeling van een gelijkaardig formulatieplatform voor slecht water oplosbare geneesmiddelen gebaseerd op organische oplossingen/suspensies met als doel 'ready-to-compress' vaste dispersies te bereiden en het oplossen en de biobeschikbaarheid van het geneesmiddel te verbeteren.

Curriculum Vitae

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"Development of solid dosage forms by co-spray drying"

European Design of Experiments User Meeting, Design Ease and Design Expert Users, CQ Consultancy, Leuven, Belgium (25/04/2006)
"Development of directly compressible powders via co-spray drying"

Spray Drying Symposium, Johnson & Johnson Pharmaceutical Research and Development, Janssen Pharmaceutica, Beerse, Belgium (14/05/2007)
"Coprocessing via spray drying as a formulation platform to improve the compactability of various drugs: Formulation development, process optimisation and scaling-up"

Oral Presentation at International Meetings

Pharmaceutical Solid State Research Cluster Symposium, University of Düsseldorf, Düsseldorf, Germany (13/09/2007)
"Coprocessing via spray drying as a formulation platform to improve the compactability of various drugs: Formulation development, process optimisation and scaling-up"

Forum of Belgian Society of Pharmaceutical Sciences, Spa, Belgium (11/10/2007)
"Coprocessing via spray drying as a formulation platform to improve the compactability of various drugs: Formulation development, process optimisation and scaling-up"

Posters Presentation at International Meetings

Spring Meeting of the Belgian-Dutch Biopharmaceutical Society, Johnson & Johnson Pharmaceutical Research and Development, Janssen Pharmaceutica, Beerse, Belgium (22/05/2006)
"Evaluation and development of directly compressible powders by co-spray drying"

Spring Meeting of the Belgian-Dutch Biopharmaceutical Society, Johnson & Johnson Pharmaceutical Research and Development, Janssen Pharmaceutica, Beerse, Belgium (22/05/2006)
"Mixture design applied to optimise a directly compressible powder produced by co-spray drying"

Solid Dosage Manufacturing Seminar, FMC Biopolymer, Brussels, Belgium (19/10/2006 – 20/10/2006)
"Development of directly compressible powders by co-spray drying"

American Association of Pharmaceutical Scientists Meeting and Exposition, San Antonio, TX, US (30/10/2006 – 02/11/2006)
"Development of directly compressible powders by co-spray drying"

Autumn Meeting of the Belgian-Dutch Biopharmaceutical Society, University of Leiden, Leiden, The Netherlands (27/11/2006)
"Effect of maltodextrin and superdisintegrant in directly compressible powder mixtures prepared via co-spray drying"

Pharmaceutical Sciences World Congress Pre-Satellite Meeting, Amsterdam, The Netherlands (20/04/2007 – 21/04/2007)
"Process design applied to optimise a directly compressible powder produced via co-spray drying"

Pharmaceutical Sciences World Congress Pre-Satellite Meeting, Amsterdam, The Netherlands (20/04/2007 – 21/04/2007)
"Evaluation of cellulose ethers in the development of directly compressible, highly dosed powders by co-spray drying"

Pharmaceutical Sciences World Congress, Amsterdam, The Netherlands (22/04/2007 – 25/04/2007)
"Process design applied to optimise a directly compressible powder produced via co-spray drying"

Pharmaceutical Sciences World Congress, Amsterdam, The Netherlands (22/04/2007 – 25/04/2007)
"Evaluation of cellulose ethers in the development of directly compressible, highly dosed powders by co-spray drying"

American Association of Pharmaceutical Scientists Meeting and Exposition, San Diego, CA, US (11/11/2007 – 15/11/2007)
"Coprocessing via spray drying as a formulation platform to improve the compactability of various drugs: Formulation development, process optimisation and scaling-up"

Scientific Publications

Development of directly compressible powders via co-spray drying
Y. Gonnissen, J.P. Remon, C. Vervaet
Eur. J. Pharm. Biopharm. 67 (2007) 220–226.

Mixture design applied to optimise a directly compressible powder produced via co-spray drying
Y. Gonnissen, S.I.V. Gonçalves, J.P. Remon, C. Vervaet
Drug Dev. Ind. Pharm. In press.

Effect of maltodextrin and superdisintegrant in directly compressible powder mixtures prepared via co-spray drying
Y. Gonnissen, J.P. Remon, C. Vervaet
Eur. J. Pharm. Biopharm. doi:10.1016/j.ejpb.2007.05.004.

Process design applied to optimise a directly compressible powder produced via a continuous manufacturing process
Y. Gonnissen, S.I.V. Gonçalves, B.G. De Geest, J.P. Remon, C. Vervaet
Eur. J. Pharm. Biopharm. doi:10.1016/j.ejpb.2007.09.007.

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
Eur. J. Pharm. Biopharm. doi:10.1016/j.ejpb.2007.11.009.

Injection moulding of sustained-release matrix tablets composed of low-substituted hydroxypropylcellulose/ethylcellulose binary mixtures.
T. Quinten, Y. Gonnissen, J.P. Remon, C. Vervaet. In preparation.

Patents

Process for preparing a solid dosage form (submitted 23 jun 2007)

Y. Gonnissen, C. Vervaet, J.P. Remon