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Research paper

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

1. Introduction

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

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

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physical mixture exhibited a predominantly elastic behaviour.

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

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

2. Materials and methods

2.1. Materials

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

2.2. Methods

2.2.1. Preparation of the spray dried microparticles

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

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

2.2.2. Evaluation of spray dried powders

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

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

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

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

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