European Journal of Pharmaceutics and Biopharmaceutics 88 (2014) 939–944

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Crystal coating via spray drying to improve powder tabletability

V. Vanhoorne, E. Peeters, B. Van Snick, J.P. Remon, C. Vervaet *

Laboratory of Pharmaceutical Technology, Ghent University, Belgium

ARTICLE INFO

Article history:
Received 23 July 2014
Accepted in revised form 29 October 2014
Available online 7 November 2014

Keywords:
Spray drying
Coprocessing
Particle coating
Direct compression
Amorphous lactose
Paracetamol
Tabletability
Continuous production

ABSTRACT

A continuous crystal coating method was developed to improve both flowability and tabletability of powders. The method includes the introduction of solid, dry particles into an atomized spray during spray drying in order to coat and agglomerate individual particles. Paracetamol was used as a model drug as it exhibits poor flowability and high capping tendency upon compaction. The particle size enlargement and flowability were evaluated by the mean median particle size and flow index of the resulting powders. The crystal coating coprocessing method was successful for the production of powders containing 75% paracetamol with excellent tableting properties. However, the extent of agglomeration achieved during coprocessing was limited. Tablets compressed on a rotary tablet press in manual mode showed excellent compression properties without capping tendency. A formulation with 75% paracetamol, 5% PVP and 20% amorphous lactose yielded a tensile strength of 1.9 MPa at a compression pressure of 288 MPa. The friability of tablets compressed at 188 MPa was only 0.6%. The excellent tabletability of this formulation was attributed to the coating of paracetamol crystals with amorphous lactose and PVP through coprocessing and the presence of brittle and plastic components in the formulation. The coprocessing method was also successfully applied for the production of directly compressible lactose showing improved tensile strength and friability in comparison to a spray dried direct compression lactose grade.

1. Introduction

Tablets are the most popular dosage form for patients as well as manufacturers because of the convenience of administration, accurate dosing, ease of manufacturing, product stability in comparison to liquids and tamper-proofness in comparison to capsules [1]. Direct compression is the preferred manufacturing method for tablets because of its simplicity, continuous nature and related financial benefits. However, it is estimated that less than 20% of pharmaceutical powders can be directly compressed into tablets as powders must have appropriate flowability, compressibility and homogeneity to be suited for direct compression [1,2].

To improve these properties coprocessing of materials is widely applied for the preparation of powder mixtures enabling direct compression of a drug substance. During coprocessing two or more components are combined by a specific process, yielding a material with superior properties compared to physical mixtures of their components, without modification of the chemical structure of the ingredients [1,3].

In this work we aimed to improve both flowability and tabletability of powders by the development of a continuous crystal coating method. The manufacturing method is based on the introduction of dry powder particles into an atomized spray during spray drying. The resulting powders were microscopically evaluated and characterized through particle size analysis, flowability testing and tableting experiments. It was first investigated whether the method allowed to produce paracetamol tablets without capping tendency via coating of paracetamol particles with spray dried lactose and polyvinylpyrrolidone (PVP). The flowability and tabletability of the resulting powders was assessed and compared to the characteristics of the corresponding physical mixtures. In a second part, it was investigated whether the method is also applicable for the production of direct compression lactose.

2. Materials and methods

2.1. Materials

Paracetamol (semi fine) was received from Mallinckrodt Chemical (Hazelwood, USA). Milled α-lactose monohydrate (Pharmatose® 200M) was purchased from Caldic (Hemiksem, Belgium).

Abbreviations: PVP, polyvinylpyrrolidone; SEM, scanning electron microscopy; LOD, loss on drying; ffc, flowability index; XRD, X-ray diffraction; MDSC, modulated differential scanning calorimetry; d_{50}, mean median particle size.

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium. Tel.: +32 9 264 80 69; fax: +32 9 222 82 36.

E-mail address: Chris.Vervaet@UGent.be (C. Vervaet).

http://dx.doi.org/10.1016/j.ejpb.2014.10.018
0939-6411/

A direct compression grade of spray dried lactose (DCL 11) was purchased from DFE Pharma (Goch, Germany). Silicon dioxide and magnesium stearate (Fagron, Waregem, Belgium) were used as glidant and lubricant, respectively. PVP and Crospovidone® were used as binder and desintegrant, respectively, and were received from BASF (Burgbernheim, Germany) . Miglyol (Cremer Oleo, Witten, Germany) with 0.2% polysorbate 80 (Fagron, Waregem, Belgium) was used as dispersant for laser diffraction measurements.

2.2. Methods

2.2.1. Preparation of the coprocessed powders

In a first set of experiments, aqueous solutions of lactose and PVP (16% and 8% w/w lactose with lactose/PVP ratio: 4/1) and of pure PVP (3% w/w) were prepared. These solutions were fed to the fountain two-fluid nozzle (nozzle orifice 2.6 mm) of a production-scale spray dryer (type 6.3-SD, GEA Niro, Copenhagen, Denmark) by a peristaltic pump (type 520U, Watson Marlow, Cornwall, UK) and marprene tubing (inside diameter 4.8 mm). The spray dryer operated in counter-current mode. The dimensions of the spray dryer were 2.0 m cylindrical height with a diameter of 3.5 m and 60° conical base. The main powder fraction was collected in a reservoir under the drying chamber and fines were collected in a reservoir attached to a cyclone. The solutions were spray dried according to the following parameters: feed rate: 100 g/min, inlet drying air temperature: 240 °C, outlet drying air temperature: 112 °C, drying gas rate: 210 kg/h, atomizing air pressure: 0.5 bar. Paracetamol was preblended with 0.05% silicon dioxide and introduced during the spray drying process into the cone of the drying chamber via an in-house designed setup shown in Fig. 1. This setup consists of a vibratory feeder (DR 100, Retsch, Haan, Germany) presenting the powder to a Venturi-based system that introduces the powder through two small tubes (internal diameter 7 mm) into the dryer. The tubes were positioned close to the nozzle and were oriented to directly inject the solid particles in the spray pattern of the atomized drops. The composition of the spray dried solutions, the feed rate of solid particle introduction and the final composition of the coprocessed powders (fraction spray dried lactose, fraction dry inserted paracetamol, content PVP) are given in Table 1.

In a second set of experiments, aqueous solutions of lactose (2.5%, 5%, 10% and 16% w/w) and PVP (0.85%, 1%, 1.25%, 0.8% w/w, respectively) and of pure PVP (0.8% w/w) were spray dried, while lactose crystals were introduced via the same procedure as described above. For spray drying of the pure PVP solution the inlet temperature was increased to 240 °C in order to ensure that the moisture content of the coprocessed powder does not exceed the moisture content of the starting material by more than 2.5%. The composition of the solutions, feed rate of solid particle introduction and the final composition of these coprocessed powders are listed in Table 2.

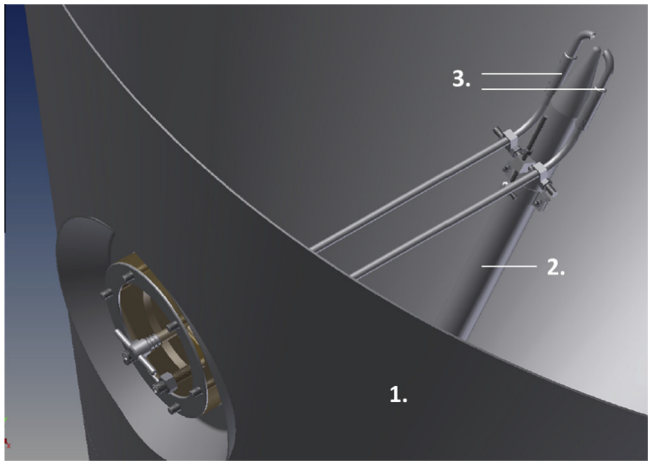

Fig. 1. Schematic of the setup that allows to directly inject solid particles into the atomization zone of a two-fluid nozzle positioned in the drying chamber of a spray dryer. 1. Wall of the drying chamber, 2. Two-fluid nozzle, 3. Tubes for dry powder injection into the spray zone. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2.2. Tableting

The coprocessed powders, physical mixtures and reference lactose (spray dried α-lactose monohydrate for direct compression) were blended (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 5% Crospovidon® and 0.5% magnesium stearate.

Tablets (500 ± 5 mg) of the coprocessed powders with paracetamol and of the corresponding physical mixtures were compressed on a rotary tablet press (MODUL™ P, GEA Pharma Systems, Courtoy, Halle, Belgium) equipped with a single round concave Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The tablets were compressed at 7 different main compression pressures: 31, 61, 104, 146, 188, 237 and 288 MPa after precompression at 18 MPa. The friability was tested on tablets compressed at 188 MPa.

The coprocessed powders consisting of lactose and PVP and the lactose reference were compressed (1 g ± 10 mg) on an excentric tablet press (Type EKO, Korsch, Berlin, Germany) equipped with 16.0 mm edged punches at a compression force of 132 MPa.

2.2.3. Material characterization

2.2.3.1. Morphology. The powders were examined by scanning electron microscopy (SEM) (JEOL JSM-5600-LV, JEOL Ltd., Zaventem, Belgium) after sputtering with a platinum coating using the JEOL JFC 1300 Autofine Coater (JEOL Ltd., Zaventem, Belgium) to improve the electron conductivity of the samples.

2.2.3.2. Loss on drying (LOD). The residual moisture content of the coprocessed powders was determined via LOD using a moisture analyzer (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) including an infrared dryer and a balance. A sample of 5 g was dried at 105 °C until the weight was constant for 30 s.

2.2.3.3. Particle size analysis. The particle size distribution of the paracetamol starting material and coprocessed powders was measured in triplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK). The wet dispersion technique was applied using the 300RF lens (Malvern Instruments, Worcestershire, UK). The powders were dispersed in a solution of 0.2% Tween 80 in Miglyol 812 and subsequently vortexed and sonicated in order to eliminate agglomerates. The results are expressed as volume diameters.

2.2.3.4. Ring shear testing. The flowability expressed as the flowability index (ffc) of the powders was measured in triplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using three consolidation stresses, 400, 600 and 800 Pa, and a preshear of 1000 Pa.

2.2.3.5. Solid state characterization. Crystallinity was analyzed using X-ray diffraction (XRD) and modulated differential scanning calorimetry (MDSC) on the pure compounds, physical mixtures and coprocessed samples. XRD was performed on a Cu Kα diffractor (ARL™ X'TRA, Thermo Fischer Scientific, Waltham, United States) with a voltage of 40 mV in the angular range of $8° < 2\theta < 60°$ using a step scan mode with step size of 0.02° and counting time of 1 s/step.