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Research Paper

Influence of small amorphous amounts in hydrophilic and hydrophobic APIs on storage stability of dry powder inhalation products

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ABSTRACT

The effects of different manufacturing methods to induce formation of amorphous content, changes of physico-chemical characteristics of powder blends and changes of aerodynamic properties over storage time (6 months) analyzed with the Next Generation Impactor (NGI) are investigated. Earlier studies have shown that standard pharmaceutical operations lead to structural disorders which may influence drug delivery and product stability. In this investigation, fully amorphous drug samples produced by spray-drying (SD) and ball-milling (BM) as well as semi-crystalline samples (produced by blending and micronization) are studied and compared to fully crystalline starting material. The amorphous content of these hydrophilic and hydrophobic active pharmaceutical ingredients (APIs) was determined using a validated one-step DVS-method. For the conducted blending and micronization tests, amorphous amounts up to a maximum of 5.1% for salbutamol sulfate (SBS) and 17.0% for ciclesonide (CS) were measured. In order to investigate the impact of small amorphous amounts, inhalable homogenous powder mixtures with very high and low amorphous content and a defined particle size were prepared with a Turbula blender for each API. These blends were stored (6 months, 45% RH, room temperature) to evaluate the influence of amorphous amounts on storage stability. The fine particle fraction (FPF: % of emitted dose < 5 μm) was determined with the NGI at defined time points. The amorphous amounts showed a major effect on dispersion behavior, the mixtures of the two APIs showed differences at the beginning of the study and significant differences in storage stability. The FPF values for SBS decreased during storage (FPF: from 35% to <27%) for the blend with high amorphous amounts, in contrast the initially re-crystallized sample achieved a comparable constant level of about 25%. For the hydrophobic CS a constantly increasing FPF (from 6% to >15%) over storage time for both types of blends was determined. Therefore, prolonged stability of amorphous parts and an incalculable behavior for CS blends are supposed, in contrast, SBS showed a controllable FPF after conditioning.

1. Introduction

Today, more and more drugs for inhalation are formulated in pharmaceutical powder form and are routinely used in the treatment of respiratory diseases [1]. For these dry powder inhalers (DPIs), which are used mainly for the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) [2], the delivery and dispersion of the powder depends on many factors. The crystallinity and the particle size of the powder are the key factors in drug stability and bioavailability [3] disregarding the patients' use of the device. Actual methods such as spray-drying, grinding, jet milling and liquid–liquid antisolvents [3] are used for drug micronization (particle size < 5 μm). These pharmaceutical operations such as milling lead to structural changes (for example amorphous regions) and thus could alter the surface properties [4]. This metastable state may change during handling, over storage time or by changes in humidity/temperature [5]. It is well documented that it could induce re-crystallization [6] of these amorphous regions and particle size changes post-production.

Primarily reducing or increasing forces of cohesion or adhesions (drug–drug or drug–carrier) depend on macroscopic properties of the particles [7]. Important parameters that have an influence on the aerosolization behavior, which may change during re-crystallization, are mainly the particle size of API and the carrier [8], but also the particle shape [9] and surface rugosity [10,11]. During milling and blending electrostatic charging [12] may occur

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causing new contact areas on particles. In the course of use, if higher relative humidity (RH) will be reached and if more water molecules are present in the powder formulation thin film layers are formed and higher capillary forces [13] are induced. Regarding the flow properties a change in physicochemical properties may influence important parameters such as binding energy and binding forces (e.g., van der Waals forces) between the detaching drug and the lactose carrier during dispersion [14].

In this study, first an impression for the extent of amorphous amounts through various production methods (spray-drying, ball-milling, blending and jet-milling) for hydrophilic salbutamol sulfate (SBS) and hydrophobic ciclesonide (CS) is given. These amorphous amounts are calculated on the basis of a one-step dynamic vapor sorption method (DVS). Finally, homogenous powder blends for inhalation containing different amounts of amorphous API are investigated during a storage stability test over a 6-month period. The intention of the study was to evaluate the impact of amorphous parts in powder formulations on the aerodynamic properties and to compare the different behavior of a hydrophobic and hydrophilic API during storage. The aerodynamic properties of the powder blends were assessed using the NGI. The focus is not set on carrier particles (type, size, drug: carrier ratio), which are typically the main component of inhalation powders, because many studies already showed the effect on lung deposition of drug [15,16].

2. Materials and methods

2.1. Materials

Crystalline salbutamol sulfate (SBS) is chosen as a hydrophilic model drug (particle size $d50 = 7.3 \pm 0.3$ µm) and crystalline ciclesonide (CS) represents the hydrophobic model drug (particle size $d50 = 57.9 \pm 3.0$ µm). The water was used of double distilled (ddH_2O) quality (GEA Diessel GmbH, Hildesheim, Germany) and methanol was supplied by J.T. Baker (Deventer, The Netherlands). The methylene chloride, for the spray-drying of CS, was supplied by Sigma–Aldrich Chemie GmbH (Steinheim, Germany). The isopropanol for the DVS measurement was supplied by AppliChem GmbH (Darmstadt, Germany). α-Lactose-Monohydrate (Respitose® SV003, $d50 = 57.9 \pm 0.2$ µm) was kindly provided by DFE pharma, Goch, Germany.

2.2. Methods

2.2.1. Ball-milling (BM)

25 g of crystalline SBS or CS was ball-milled in zirconium oxide grinding jars (500 ml) containing 6 (SBS) or 4 (CS) zirconium oxide grinding balls (30 mm) using a Retsch PM 100 mill (Haan, Germany). The grinding time was set to 24 h (SBS) and 2 h (CS), rotation speed was 450 rpm (SBS) and 350 rpm (CS), respectively. During the process the temperature (cold storage room: 1–3 °C) was monitored. The amorphous samples (ball-milled powders) were stored over P_2O_5 in a desiccator (volume 2.4 l, room temperature) to avoid re-crystallization. In the following these powders were used for the trials with DVS and for the preparation of blends.

2.2.2. Spray-drying (SD)

Amorphous SBS was also prepared by spray drying of a 5% (w/w) aqueous solution with a Büchi Mini Spray Dryer B-290 (Flawil, Switzerland). An inlet air temperature of 150–151 °C, an outlet temperature of 80–82 °C, feed flow of 4.5 ml/min and an aspiration of 100% were used.

Amorphous CS was prepared by spray drying of a 5% (w/w) methylene chloride solution at an inlet air temperature of 50–51 °C, an outlet temperature of 34–35 °C, feed flow of 3.75 ml/min and an aspiration of 100%. To avoid re-crystallization the amorphous samples were stored over P_2O_5 (desiccator: volume 2.4 l, room temperature). In the following these powders were used for DVS measurements.

2.2.3. Jet-milling (JM)

5 g of crystalline SBS or CS was jet-milled (JM1) using the Jet-O-Mizer Modell 00 (Fluid Energy Aljet, Plumsteadville, USA). The grinding pressure was adjusted to 8.0 bar and three grinding cycles (GC 1–3) were performed. To avoid re-crystallization the amorphous samples were stored over P_2O_5 (desiccator: volume 2.4 l, room temperature). In the following these powders were used for DVS measurements and the powders with three grinding cycles were used for preparation of powder blends and analyzed with the Next Generation Impactor.

2.2.4. Mixing test

The powder blends with micronized, crystalline API (1 g) and glass beads (24 g, 0.25 mm or 4.0 mm, Roth, Karlsruhe, Germany) were accurately weighed into a stainless steel container by using the double sandwich method. All blends were prepared with a Turbula blender (W.A. Bachofen AG, Basel, Switzerland). The mixing speed (42 rpm) and the mixing time (45 min) have been retained unchanged.

After the blending process the glass beads were separated by an air jet sieve and cyclone (Hosokawa Alpine, Augsburg, Germany). In the following these powders were used for DVS measurements.

2.2.5. Blending calibration curve (CC)

Powder blends with amorphous ball-milled SBS or CS (0.25%, 2.0%, 5.0%, 8.0% and 15.0%) and crystalline API were firstly sieved (mesh size: 500 µm) and then accurately weighed into a stainless steel container by using the double sandwich method. All blends were prepared with a Turbula mixer (W.A. Bachofen AG, Basel, Switzerland). The mixing speed (42 rpm) and the mixing time (3×15 min and after every 15 min sieved with the 500 µm sieve) have been retained unchanged. In the following these blends were used to calculate the amorphous amounts.

2.2.6. Study design – storage stability

In this investigation the same α-Lactose-Monohydrate is used for all four mixtures, only the API and amorphous contents are changed. In both designs of storage stability (Fig. 1) processing parameters such as micronization or blending (grinding pressure, grinding cycles, type of mixer, mixing speed, mixing time and batch size), drug content (drug-to-carrier ratio of 1:100), drug properties (particle size) and storage conditions (6 months, 45% RH, room temperature) are identical. To re-crystallize parts of the amorphous amounts of both APIs (SBS_2 und CS_2), a conditioning time was chosen which did not lead to changes in particle size. Therefore, both APIs still had a measurable residue of amorphous parts.

2.2.7. Conditioning of the APIs

To avoid re-crystallization after the milling process half of the amorphous samples were stored over P_2O_5 in a desiccator (SBS_1 and CS_1). The other half of hydrophobic CS was stored over 10 ml isopropanol for 2 h (CS_2) and the other half of hydrophilic SBS was stored over saturated KCl solution at 85% RH for 16 h (SBS_2) in order to re-crystallize the main amorphous parts (volume: 2.4 l).

2.2.8. Blending powder for inhalation

Powder blends with micronized amorphous or crystalline API (SBS_1/SBS_2 or CS_1/CS_2, 0.25 g) and α-Lactose-Monohydrate