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How does secondary processing affect the physicochemical properties of inhalable salbutamol sulphate particles? A temporal investigation

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ABSTRACT

As pulmonary drug delivery is extended from low doses to high doses, physicochemical characteristics of the active pharmaceutical ingredient gain importance in the development of dry powder inhalers. Therefore, the present work aims to understand the impact of distinct engineering techniques on the process induced physicochemical characteristics of salbutamol sulphate particles over time. The particle engineering techniques chosen were jet-milling and spray-drying, two well used processes in the production of predominately crystalline and amorphous inhalable particles, respectively. Fourier transform infrared spectroscopy, modulated differential scanning calorimetry, particle size distribution and tensiometry experiments were used to characterise the engineered powders immediately, 7, 14 and 21 days after production. The rugged spherical amorphous particles ($3.75 \pm 0.08\ \mu m$) obtained via spray-drying showed that they were capable of forming strong agglomerates ($5.01 \pm 0.22\ \mu m$) through "amorphous bridging". On the other hand, jet-milling produced smaller ($2.06 \pm 0.08\ \mu m$), crystalline, irregular shaped particles with a very large surface area ($11.04 \pm 0.10\ m^2/g$) that, over time, formed looser particle aggregates of decreasing size ($3.76 \pm 0.10\ \mu m$). Temporal evolution of the properties of spray-dried and jet milled particles showed a notable influence on the efficiency of blending with a model carrier at 0, 7 and 21 days (e.g. relative standard deviation of drug content of 11.3, 7.0 and 21.6%, respectively).

1. Introduction

Dry powder inhaler (DPI) products are powder formulations used to deliver active pharmaceutical ingredients (API) via inhalation to the lung. In order to deposit in the lung, API particles are generally required to have an aerodynamic diameter of 1–5 μm. Particulate materials of such size pose a challenge in handling, processing and product performance, due to their poor flowability. Therefore, a common formulation strategy is the use of larger excipient carrier particles - usually sugars such as lactose or mannitol - in order to improve product performance (Pilcer et al., 2012). These dosage forms are called carrier based-DPI platforms and represent the majority of DPI products available on the market. Salbutamol sulphate, a short acting β_2-agonist, is prescribed for the treatment of bronchospasm and COPD (Labiris and Dolovich, 2003). The use of salbutamol sulphate in inhalation studies in recent years makes it an ideal model API, as a plethora of physicochemical information can be found in existing data (Brodka-Pfeiffer et al., 2003; Grisedale et al., 2011; Littringer et al., 2013; Zellnitz et al., 2015). This study aims to complement the current knowledge, exploring the impact of secondary processing on the physicochemical properties of salbutamol sulphate over time.

In order to be formulated into a DPI product, salbutamol sulphate particles must be engineered to the inhalable size (secondary processing). Milling is currently the most common technique to generate particles in the 1–5 μm size range and different milling techniques are available (Telko and Hickey, 2005). During milling, a mechanical force is applied to a solid material leading to its particle size reduction. It is reported that such a process can disrupt the crystalline phase, producing random domains of various molecular disorder, in particular, amorphous ones (Shur et al., 2013). Air jet milling is a well-established technique used in the manufacturing of inhalation products. In this case, an air jet stream is used, causing particle acceleration, impact,

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self-attrition, fracture and consequent size reduction (Shariare et al., 2011). Alternatively, spray-drying is a one step process also frequently applied in the pharmaceutical industry, where a solution or suspension is converted into a solid powder. In this process, a liquid is atomised into a gas stream, dried at elevated temperatures and the formed solid particles are then separated from the gaseous phase and recovered (Chow et al., 2007). The rapid solvent evaporation during the process enables the dynamic arrest of molecular motions of the API, below the glass transition temperature (Tg), originating an amorphous phase (Paudel et al., 2013). Even though the size of the generated particles is dependent on many factors, spray-drying has proven to be a suitable technique for the production of inhalable sized particles (Chawla et al., 1994; Littringer et al., 2013; Vehring, 2008).

Pharmaceutical molecules can exist in an assortment of solid-state phases – e.g. crystals, salts, cocrystals and amorphous form. Usually, in inhalation products, API particles are used in their most stable crystalline form. Research on delivering APIs in their amorphous phase is mostly driven by the development of new oral dosage forms, but has also recently raised the interest of pulmonary drug delivery researchers, in particular in the delivery of biological molecules (Chen et al., 2016). Thus, amorphisation of therapeutic molecules may, on the one hand, represent an attractive drug development approach by improving solubility and bioavailability. On the other hand, it can be an unintended consequence of the manufacturing process and can cause a deleterious effect on product performance and stability (Priemel et al., 2015). Indeed, it is known that engineering techniques can lead to changes in the solid-state of materials such as the production of different crystal phases (Tantry et al., 2007; Vanhoorne et al., 2016) or loss of crystallinity (Della Bella et al., 2016; Hancock and Zografi, 1996). Concerning the impact of different engineering techniques Shur et al. (2013), compared two processes to obtain budesonide in the inhalable size, jet-milling and sono-crystallisation, finding that the micronised material possessed process-induced surface disorder, which was not observed for the sono-crystallised one. These surface disorders revealed to impact aersolisation, as the micronised material showed worse performance than the engineered one, when tested in lactose blends. Early on using salbutamol sulphate Ward and Schultz, 1995 found that jet-milling induced the formation of amorphous domains and hypothesized that this could be deleterious in the effectiveness of inhalation products. Recently Müller et al. (2015) confirmed these former findings, showing that over time storage (45% RH and ambient temperature) led to a decrease in the fine particle fraction (FPF) of salbutamol sulphate blends with lactose monohydrate when partially amorphous particles were used. No difference was found in salbutamol sulphate FPF over time when crystalline particles were investigated. In another study where salbutamol sulphate particles were tested without the presence of carrier particles, Shariare et al. (2011b), found that the batch containing a higher percentage of amorphous content showed higher FPF. The authors attributed this to the marked cohesion between API particles and the resulting formation of larger-sized aggregates that could be fluidized.

With the increasing interest in the shift from low API doses to high doses in pulmonary drug delivery, drug physicochemical characteristics will, undoubtedly, take on an increasing importance,where final quality attributes of the product are concerned (Hoppentocht et al., 2014). Studies comparing amorphous and crystalline salbutamol sulphate powders are rare and they predominately focus on the impact of environmental conditions on particles' stability. By controlling the environmental conditions, keeping their influence to a minimum, the authors aim to investigate the possible effect and change of different process-inherited physicochemical properties over time. Therefore, two distinct well used engineering techniques in inhalation, jet-milling and spray-drying, were chosen to produce crystalline and amorphous particles of salbutamol sulphate, respectively. The target specification for the manufactured particles was an inhalable size range between 1 and 5 μm. To further assess the impact that the distinct particle properties encountered might have in terms of product development, a standard blending procedure with a model carrier, mannitol (a sugar with low propensity to form crystal hydrates, known hemihydrate is formed only when the former is freeze-dried (Alqurshi et al., 2016)), was performed and the quality and homogeneity of the mixture tested at different time points and its respective outcomes were compared.

2. Materials and methods

2.1. Materials

The model API salbutamol sulphate was supplied by Selectchemie (Switzerland, purity 99.5%) and the model carrier material Pearlitol 160® (β-mannitol, purity 99.2%, by Roquette (France). Purified water (TKA Wasseraufbereitunssysteme GmbH, Germany), diiodomethane (99%, Alfa Aesar, USA), ethylene glycol (Emplura®, Merck Millipore, USA), 1- Hexanesulfonic acid sodium salt (≥98%, Sigma-Aldrich, USA), acetic acid (Emprove®, Merck Millipore, USA) and methanol (HPLC grade, Sigma-Aldrich, USA) were also used in the experiments during the present work.

2.2. Particle engineering

An aqueous solution of salbutamol sulphate with a solid content of 7.5% (w/w) was sprayed using an atomising intensity of 0.3 ml/min and an air flow rate of 110 l/min, into a long drying chamber of a B-90 Nano Spray Dryer (Büchi Labortechnick AG, Switzerland). To obtain particles in the inhalable size range, a spray head mesh of 7 μm, an inlet temperature of 120 °C and an outlet temperature of 49 °C were used (Littringer et al., 2013). Jet-milling of salbutamol sulphate was performed in a 50 AS spiral jet mill (Hosokawa Alpine, Germany) with compressed air, using an injection pressure of 8.0 bar and a milling pressure of 5.0 bar.

2.3. Powder characterisation

The produced powders were characterised immediately, and 7, 14 and 21 days after production. In order to minimise the impact of storage conditions, the engineered samples were stored in closed plastic vials in a low humidity environment (18 ± 2% RH) at room temperature (22 ± 2 °C), controlled using a Thermo-Hygrograph (Opus 10®, Lufft, Germany) (Grisedale et al., 2012).

2.3.1. Fourier transform infrared spectroscopy

Spectroscopic analysis ($n = 3$) was carried out using an ATR-FTIR (Vertex 70, Bruker, USA). Spectra were collected in between 4000 and 400 cm^{-1} range, at a resolution of 2 cm^{-1} and 64 scans (about 5 min per measurement). The analysis was carried out under ambient conditions (22 ± 2 °C, 61 ± 6% RH). Spectral analysis was performed using Opus® software version 6.5 (Bruker, USA) and a spectral environmental compensation algorithm was applied.

2.3.2. Modulated differential scanning calorimetry

A sample of 2–4 mg ($n = 2$) was accurately weighed (XP205, Mettler Toledo, USA) and placed into a hermetically sealed aluminium pan. Modulated differential scanning calorimetry analysis (204 F1 Phönix, Netzsch, Germany) was performed using a heating rate of 5 °C/min from 25 °C to 230 °C and a modulation amplitude of ± 0.53 °C every 40 s. Nitrogen was used as a purging