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Research Paper

Measurement of low amounts of amorphous content in hydrophobic active pharmaceutical ingredients with dynamic organic vapor sorption

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ABSTRACT

Today, a variety of devices for dry powder inhalers (DPIs) is available and many different formulations for optimized deposition in the lung are developed. However, during the production of powder inhalers, processing steps may induce changes to both, the carrier and active pharmaceutical ingredients (APIs). It is well known that standard pharmaceutical operations may lead to structural changes, crystal defects and amorphous regions. Especially operations such as milling, blending and even sieving generate these effects. These disorders may induce re-crystallization and particle size changes post-production which have a huge influence on drug delivery and product stability.

In this study, pilot tests with a polar solvent (water) and hydrophilic drug (Salbutamol sulfate) were performed to receive a first impression on further possible implementation of hydrophobic samples with organic solvents. Thereafter, a reliable method for the accurate detection of low amounts of amorphous content is described up to a limit of quantification (LOQ) of 0.5% for a hydrophobic model API (Ciclesonide). The organic vapor sorption method which is a gravimetric method quantifies exactly these low amounts of amorphous content in the hydrophobic powder once the suitable solvent (isopropanol), the correct p/p_0 value (0.1) and the exact temperature (25 °C) have been found. Afterward it was possible to quantitate low amorphous amounts in jet-milled powders (0.5–17.0%).

In summary, the data of the study led to a clearer understanding in what quantity amorphous parts were generated in single production steps and how variable these parts behave to fully crystalline material. Nevertheless it showed how difficult it was to re-crystallize hydrophobic material with water vapor over a short period. For the individual samples it was possible to determine the single humidity at which the material starts to re-crystallize, the behavior against different nonpolar solvents and the calculation of the reduction of the glass transition temperature (T_g) according to the Gordon–Taylor equation.

1. Introduction

Dry powder inhalers (DPIs), pressurized metered dose inhalers (pMDIs) and nebulizers play the main role in the treatment of pulmonary diseases, each class with its unique strengths and weaknesses [1]. For the DPI there is a complex interplay between the device, the excipients, micronized active pharmaceutical ingredient (API) and the patient use [2]. A significant importance takes the API, which is typically synthesized as crystalline solid, further processed to a micronized powder with a particle size smaller than 5 μm and afterward blended with excipients to an adhesive mixture. It is well known that these standard pharmaceutical operations, such as milling [3], blending and even sieving, may lead to structural disorders or change the orientation of molecules on the surface of powder particles, and thus alter the surface properties [4]. It has been shown in numerous publications that this surface energy can be linked to interactions [5]. Furthermore it was determined that amorphous regions are created especially to the surface during energetic processes. These regions have a huge potential to change during handling and storage and should be limited to a minimal level. The metastable state is prone to change over time, initiated by changes in relative humidity and/or temperature [6].

Despite this knowledge, there are hardly any reasonable methods up to 0.5% accuracy for the detection of minimal amorphous parts [7] especially for many APIs that are more hydrophobic in nature. It is well documented in the literature how to quantify

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amorphous parts in hydrophilic samples by water moisture sorption isotherms [8]. In their review Sheokand et al. divided the DVS-methods into three main groups for the quantification of amorphous amounts [9]. Equilibrium moisture uptake (based on absorption), water uptake method (based on re-crystallization) and residual weight (based on solvated solvent) method are focused. But for hydrophobic material, which is much more chemically stable against water vapor and the change in crystallinity is self-limiting [10], only a few approaches (DVS) are available which focused on organic solvents. For example Mackin at al. used acetone as a solvent (for benzyl ether derivative) and Samra et al. used mixtures of ethanol/water and ethanol/*n*-propanol in their investigations with hydrophobic terfenadine [4,10]. The aim of this study was primarily to find the solvent with the highest affinity to the sample. Finally, the method is simplified as much as possible due to a one-step measurement (time saving: less than two days). The individuality is its biggest advantage, this method can be adapted to many active pharmaceutical ingredients (adjustment of temperature, vapor p/p_0 and screening of the solvent). Over the years different papers were published using traditional analytical techniques such as Powder X-ray Diffraction (XRPD) and Differential Scanning Calorimetry (DSC) [11]. Because of the missing sensitivity for low amorphous content (limit of detection: 5-10%) these techniques are impracticable for this purpose. Furthermore studies using isothermal microcalorimetry (IMC) were published (limit of detection: 1%) [5]. One disadvantage of this technique is that recrystallization of amorphous solid may not be detected, due to the time required to equilibrate the sample [4]. This equilibration process in the isothermal microcalorimetry takes place unmonitored for nearly 1 h. Furthermore, no data can be recorded confirming that amorphous amounts remain stable in this period of time. In comparison with the DVS drying phase (for nearly 20 h) which is monitored and recorded data (actual value is compared to target value) with regard to temperature stability (25 °C) and humidity stability (0%) amorphous amounts may show no re-crystallization. Finally near infra-red spectroscopy (limit of detection: 1%, [12]) is used to differ between amorphous and crystalline states from the evaluation of peak intensity and shifts in the known fingerprint regions of the spectra [13].

In this paper we firstly investigated crystalline, semi-crystalline and amorphous powders of hydrophilic (Salbutamol sulfate) and hydrophobic (Ciclesonide) materials by water-based DVS measurement (DVS A) and develop based on these data a new reliable and robust method after an individual organic solvent screening. Methanol, ethanol, isopropanol and ethyl acetate should give a better understanding how the hydrophobic powder behaves at different conditions (DVS B). Furthermore it was possible to calculate the lowered T_g (Gordon–Taylor equation) for each solvent and to detect the re-crystallization event for strongly nonpolar solvents. After finding the suitable non-aqueous plasticizer for ciclesonide [14], in this case isopropanol, different vapor pressures were tested (0.10 p/p_0, 0.15 p/p_0, 0.20 p/p_0 and 0.30 p/p_0) in DVS C. Furthermore the temperature was evaluated (20 °C, 25 °C and 30 °C) in a Design of Experiment (DVS D). The influence of particle size was also investigated and ultimately the method was validated (based on ICH guideline Q2 (R1)). The investigated powder samples are jet-milled at different grinding pressures and grinding cycles. These samples are compared to the crystalline starting material and to fully amorphous spray-dried and ball-milled samples.

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 used was of double distilled (ddH_2O) quality (GEA Diessel GmbH, Hildesheim, Germany). The methylene chloride, for the spray-drying of CS, was supplied by Sigma-Aldrich Chemie GmbH (Steinheim, Germany). The solvents for the organic screening ethanol and ethyl acetate, reagents for HPLC analysis of chromatography quality, were supplied by Merck KGaA (Darmstadt, Germany), methanol supplied by J.T. Baker (Deventer, The Netherlands) and isopropanol supplied by AppliChem GmbH (Darmstadt, 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 water (DVS A), the solvent screening (DVS B) and for the preparation of blends.

2.2.2. Spray-drying (SD)

Amorphous SBS was produced 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%. The amorphous samples (spray-dried 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 water (DVS A) and in the solvent screening (DVS B).

2.2.3. Jet-milling (JM)

5 g of crystalline CS (JM1) was jet-milled 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. 5 g of crystalline CS was also jet-milled at 2 bar (JM2), 3 bar (JM3) and 4 bar (JM4) grinding pressure, respectively, by applying only one grinding cycle (GC1). In general, the amorphous samples (micronized powders) were stored over P_2O_5 in a desiccator (volume 2.4 l, room temperature) to avoid re-crystallization. These samples were hereinafter used for the measurements with different isopropanol vapor pressures (DVS C), the evaluation of the temperature (DVS D), the test of precision/repeatability and to show effects of particle size.

2.2.4. Blending different amorphous amounts

Firstly, powder blends with amorphous ball-milled API (0.1%, 0.15%, 0.2%, 0.25%, 0.5%, 2.0%, 5.0%, 8.0% and 15.0%) and crystalline API were 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 blender (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 a 500 µm sieve) were kept constant for all blends. These blends were used in the comparison of different methods (DSC, mDSC, Hyper-DSC and XRPD), for the determination of limit of