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Nano- and Microstructured model carrier surfaces to alter dry powder inhaler performance

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A B S T R A C T

The present study investigates the effect of different carrier surface modifications on the aerosolisation performance and on the effective carrier payload of interactive blends for inhalation. Two different active pharmaceutical ingredients (APIs) were used: Formoterol fumarate dihydrate (FF) and budesonide (BUD). Blends were prepared with glass beads as model carriers which have been subjected to mechanical surface modifications in order to introduce surface roughness via treatment with hydrofluoric acid (HF) and/or milling with tungsten carbide (TC).

As far as effective carrier payload, in this study expressed as true surface coverage (TSC), is concerned, surface modification had varying effects on blends containing BUD or FF.

Aerodynamic characterisation in vitro showed a significant decrease in respirable fraction for glass beads treated with HF (40.2–50.1%), due to the presence of clefts and cavities, where drug particles were sheltered during inhalation. In contrast, grinding with TC leads to surface roughness on a nano scale, ultimately increasing aerodynamic performance up to 20.0–38.1%. These findings are true for both APIs, regardless of their chemical properties.

1. Introduction

Dry powder inhalers (DPIs) are an important tool in the treatment of respiratory diseases like asthma bronchiale or chronic obstructive pulmonary disease (COPD). To reach the deeper parts of the lungs, a micronised API in the size range of 1–5 μm (aerodynamic particle size) is required (Bosquillon et al., 2001; Labiris and Dolovich, 2003). Since those medicines are highly potent, the delivery of only a very low dose (BUD: 200–800 μg; FF: 6–12 μg) is needed. However, small particle size and low quantity of powder are generally critical parameters leading to poor flow properties, agglomeration and deteriorated metering of dose. Therefore, the API is oftentimes blended with coarse carrier particles in order to enhance powder flowability and dosing characteristics as well as dispersibilty (Le et al., 2012).

The effectiveness with which the drug is delivered to its target site is influenced by a variety of factors concerning the carrier. Previous studies have investigated, inter alia, the effect of particle size (Steckel and Mueller, 1997; Guenette et al., 2009) and shape (Kaialy et al., 2011), carrier payload (Young et al., 2011), amorphicity (Harjunen et al., 2002) and polymorphic forms (Kaialy and Nokhodchi, 2013).

Furthermore, factors unrelated to the powder blend itself impact the lung deposition profile. Design of the inhalation device (Coates et al., 2004), humidity (Price et al., 2002) and patient's inhalation behaviour (Chew, 2000) also have to be taken into account. Another factor found to have a crucial effect on lung deposition is the carrier surface topography/microstructure. It influences interparticulate interactions between carrier and API and therefore drug detachment. The main interaction forces between the two components in interactive mixtures are van der Waals forces (Concessio et al., 1999) and triboelectric forces (Karner et al., 2014). On the one hand, the attractive forces have to be sufficiently high to maintain adequate blend stability and reliable blend homogeneity. Furthermore, a high level of attractive forces generally secures major carrier payload, which has been shown to improve the respirable fraction (Young et al., 2011). Therefore this study also investigated the effective carrier payload, expressed as the true surface coverage (TSC), on aerodynamic performance.

However, these forces need to be low enough for drug detachment to take place during the inhalation maneuvre. Since

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low drug delivery in DPIs is often due to insufficient separation of carrier and API resulting from excessive adhesion forces, these have to be carefully balanced. So far, contrary results concerning the effect of carrier surface topography, more precisely surface roughness, have been published. While Chan et al. (2003) experienced an optimal drug detachment when using carriers holding a rough surface, Zeng et al. (2000) and Iida et al. (2004) achieved an enhanced aerodynamic performance with blends containing carrier particles with smoothed surfaces. These contradicting results might be partly reasoned in an unclear definition of "rough" and "smooth" surfaces. Equally important seems the fact that relevant variables concerning formulation and inhalation device potentially interact with each other. Dickhoff et al. (2005) experienced this phenomenon discovering a stronger influence of carrier payload on drug detachment for smoother carrier surfaces compared to carriers with a substantial carrier roughness. Furthermore, de Boer et al. (2003) described a (slight) increase in carrier residue when using carriers with rough surfaces compared to smooth particles at a low flow rate of 30 L/min, while they found the effect of surface roughness being practically negligible at 60 L/min.

This study aims to provide a systematic approach to this scientific question by introducing different types of surface roughness on the carriers. Instead of the conventionally used lactose (Kou et al., 2012) or mannitol, which is gaining in importance lately (Kaialy and Nokhodchi, 2015), glass beads (GBs) in the size range of 400–600 μm were used as model carriers. Although GBs are very different from typical carrier materials in terms of crystallinity, density and shape, the great advantage is the fact, that they can easily be surface modified without changing their actual size or overall shape providing the opportunity to investigate only the effect of that corresponding modification without any changes of other carrier surface properties possibly influencing the result. This is beneficial, since those factors have already been proven to effect interparticle interactions, as mentioned earlier.

Previous studies investigating the effect of carrier surface properties have mainly focused on salbutamol sulfate as API (Littringer et al., 2012; Chan et al., 2003). In the present study, Budesonide (BUD) served as hydrophobic model drug, while Formoterol fumarate (FF) was used as its more hydrophilic counterpart. Both APIs were spray dried to create uniform particles with comparable size and shape. By using carrier and API particles that are both spherical, it was possible to calculate the amount of API needed for different carrier payloads (calculated as the amount needed to cover different percentages of carrier surface), in this study expressed as calculated surface coverages (CSC).

As previously mentioned, drug loading can also have a substantial effect on the aerodynamic performance. Other authors attributed this observation to the presence of so called 'active sites', where drug particles preferably bind to upon blending (Hersey, 1975; Staniforth, 1995). The presence of these highly energetic spots might not only be ascribed to chemical properties on the carrier surface but also to morphological characteristics (El-Sabawi et al., 2006).

This study was designed to investigate the impact of varying carrier surface topographies on the deposition profile and fine particle fraction of two drugs routinely used for inhalation, which differed in their physico-chemical properties. The obtained data should ultimately facilitate the tailoring of interparticle interactions between carrier and API to reach optimal aerodynamic performance.

2. Materials and methods

2.1. Materials

Glass beads (SiLibeads® Type S, ×50 = 534.4 μm ± 13.1 μm) were provided by Sigmund Lindner GmbH (Warmensteinach, Germany). Micronized budesonide was purchased from Minakem SAS (Dunkerque, France). Micronised formoterol fumarate dihydrate was provided by Boehringer Ingelheim (Ingelheim, Germany). Tungsten carbide (nominal grain size: 25 μm) was provided by Wolfram Bergbau und Huetten AG (St. Martin i.S./ Austria). All other chemicals were of analytical grade and have been purchased from common suppliers.

2.2. Modification of glass beads

Prior to modification, untreated glass beads (GB_UT) were cleaned with Piranha solution ($3{:}7 = H_2O{:}H_2SO_4$) followed by a standard clean ($1{:}1{:}5 = H_2O_2{:}NH_4OH{:}H_2O$). Afterwards, glass beads were incubated with hydrofluoric acid (HF) for 10 min and thoroughly rinsed with purified water for several times (HF10 min). One batch each of these glass beads was then ground with tungsten carbide (TC) in a Retsch PM 100 ball mill (Retsch GmbH, Haan, Germany) for four and eight hours, respectively (HF + TC4 h and HF + TC8 h). Additionally, untreated glass beads were treated with TC for four and eight hours as well (TC4 h and TC8 h). TC remaining on glass surfaces was removed in an ultrasonic bath by washing with purified water.

2.3. Scanning electron microscopy (SEM)

Samples were prepared by applying a thin layer of probe onto a carbon sticker which was glued on top of a metal specimen holder. The samples were sputtered with gold atoms using a BAL-TEC SCP 050 Sputter Coater (Leica Instruments, Wetzlar, Germany) and analysed with a Zeiss Ultra 55 Plus (Carl Zeiss NTS GmbH, Oberkochen, Germany) working at a voltage of 2 kV and equipped with a SE-2 detector.

2.4. Atomic force microscopy (AFM)

Prior to analysis, glass beads were fixed onto a glass slide using a two-component adhesive (UHU, Buehl, Germany). Determination of surface roughness as well as imaging was performed with a JPK NanoWizard I (JPK Instruments AG, Berlin, Germany) equipped with an OMCLAC 160 TN-W2 cantilever (Olympus, Tokyo, Japan). For every type of glass bead 3 areas of 100 μm^2 (10 μm × 10 μm) on 3 different glass beads were measured with tapping mode imaging. From the resultant data, carrier surface roughness, expressed as the root mean square roughness (R_{rms}), was determined using Gwyddion 2.42 data analysis software (Gwyddion Open Source Software, supported by Czech Metrology Institute, http://gwyddion.net/). R_{rms} was calculated based on equation 1, where n is the number of data points and x_i being the vertical distance of the *i*th data point from the mean value of the corresponding scan line (Klapetek et al., 2012). In order to take the effect of overall curvature out of the equation, it was subtracted from each AFM picture before the actual calculation.

$$R_{rms} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} x_i^2} \quad (1)$$

2.5. Spray drying of APIs

To generate spherical API particles, BUD and FF were dissolved in methylene chloride and methanol, respectively, and processed