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# Preparation and characterization of physically modified glass beads used as model carriers in dry powder inhalers

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ABSTRACT

The aim of this work is the physical modification and characterization of the surface topography of glass beads used as model carriers in dry powder inhalers (DPIs). By surface modification the contact area between drug and carrier and thereby interparticle forces may be modified. Thus the performance of DPIs that relies on interparticle interactions may be improved. Glass beads were chosen as model carriers because various prospects of physical surface modification may be applied without affecting other factors also impacting interparticle interactions like particle size and shape. To generate rough surfaces glass beads were processed mechanically by friction and impaction in a ball mill with different grinding materials that were smaller and harder with respect to the glass beads. By varying the grinding time (4 h, 8 h) and by using different grinding media (tungsten carbide, quartz) surfaces with different shades of roughness were generated. Depending on the hardness of the grinding material and the grinding time the surface roughness was more or less pronounced. Surface roughness parameters and specific surface area were determined via several complementary techniques in order to get an enhanced understanding of the impact of the modifying procedure on the surface properties of the glass beads.



## 1. Introduction

Dry powder inhalers (DPIs) are medical devices used in the treatment of COPD and asthma. The formulations used in DPIs typically consist of adhesive mixtures of the active pharmaceutical ingredient (API) and a carrier. In order to reach the tiny airways of the deep lung the API particles have to exhibit an aerodynamic diameter of 1–5 μm. Particles of this size are rather cohesive and show poor flow properties and dosing (Daniher and Zhu, 2008). That is why carrier based formulations, in which the API is attached to the surface of coarser carrier particles (50–200 μm), have been invented. Due to the size and adequate flowability of the carrier the adhesive mixtures of the drug and the carrier exhibit satisfactory flowability. Drug detachment from the carrier during inhalation is necessary to ensure that the drug particles reach their targeted site, the deep lung. Otherwise they will impact together with the coarse carrier on the upper airways. Therefore, interparticle interactions play a crucial role in carrier based formulations. It is important, that they are on the one hand high enough that uniform dosing is possible and on the other hand low enough that drug detachment during inhalation is guaranteed.

The carrier particles commonly used are lactose or mannitol. As the surface topography largely affects interparticle interactions, different attempts to modify the surface topography of carrier particles to improve the performance of DPIs and increase the fine particle fraction (FPF) were reported. These attempts include crystallization of lactose particles from different media and under different crystallization conditions (Larhrib et al., 2003; Zeng et al., 2000a,b, 2001a,b), particle smoothing by coating lactose particles with aqueous lactose solutions (Chan et al., 2003; Iida et al., 2005), and dispersion of the carrier material in a dispersion media and subsequent elimination of the dispersion media (Dickhoff et al., 2006; El-Sabawi et al., 2006; Iida et al., 2001, 2003; Islam et al., 2004a,b), which is also a method to smoothen particles. Also the addition of fine carrier particles or fine ternary components was documented as a method to alter the surface topography by occupying high energy sites on the carrier or by forming multiple agglomerates (Adi et al., 2006, 2007; Guchardi et al., 2008; Iida et al., 2004a,b; Louey and Stewart, 2002; Louey et al., 2003; Podczeck, 1999; Tee et al., 2000; Zeng et al., 2001b). Spray drying was described to be a suitable method to generate mannitol particles with modified

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**Fig. 1.** Impact of surface roughness on interparticle interactions. Depending on the shade of the surface roughness meaning the distance between the roughness peaks and valleys the contact area can be altered and thus interparticle interactions.

surface roughness (Littringer et al., 2012; Maas et al., 2011). Other attempts implement the effect of mechanical stress on lactose surface properties e.g. wet smoothing in a high shear mixer (Ferrari et al., 2004), particle smoothing with a high speed mixer in the presence of a small amount of wetting solvent (Young et al., 2002), surface processing with a high speed elliptical-rotor type powder mixer (Iida et al., 2004c), as well as milling lactose with various mill speeds to avoid batch to batch variability and to make carrier particles homogenous (Steckel et al., 2006). However, in most of these cases beside the surface topography also other properties impacting interparticle interactions, like particle size or shape of the carrier particles, ere altered. For example, recently, Maas reported carrier surface modification of mannitol by spray drying at different conditions (Maas, 2009). Spray drying changed the surface roughness, however, the particle shape changed as well. In the present work glass beads are used as model carriers. Nevertheless beneath surface roughness particle shape changed as well. That is why the model carriers used in the present work are glass beads. The glass beads have ideal geometry, they are available in different sizes and, most importantly, they allow various prospects of surface modification, without affecting other properties like particle size and shape. However it has to be mentioned that glass beads are neither typical nor conventional carrier particles. They are used as model carriers and the aspect of inhalation toxicity has to be considered if applying the inhalate to the patient finally. Particles in the size of the glass beads (400–600 μm) used in this study are too big to be inhaled. Instead they will impact in the mouth and throat and will be swallowed. Nevertheless if glass beads are considered to be applied as carrier particles in DPI formulations, a new type of inhaler with a particular restraining mechanism for the glass beads has to be designed.

There are different and contradictory findings related to the correlation of particle roughness and fine particle fraction (FPF). For example Kawashima documented that the rougher the carrier particles the lower the FPF (Kawashima et al., 1998). The surface roughness in that study resulted from crevices on the lactose surface. By contrast, Chan reported that rougher lactose carrier particles lead to a higher fine particle fraction (Chan et al., 2003). In that study the surface roughness resulted from the presence of immobilized lactose fine particles on the surface that lead to microscopic undulations on the lactose surface rather than to crevices. These contradictory findings illustrate that it has to be differentiated between roughnesses and that in order to increase the FPF the right kind of surface roughness has to be introduced. As Young (Young et al., 2008) already reported and as Fig. 1 shows, the shade of surface roughness compared to the size and shape of the API largely impacts interparticle interactions and thus drug detachment and FPF. According to that, carrier particles with increased surface area and increased surface roughness pursuant to Fig. 1C lead to higher FPFs and increase the efficiency of DPIs (Kawashima et al., 1998).

Therefore the aim of the present work was to physically modify the surface roughness of glass beads intended for use as carrier particles in DPIs. Carrier particles with increased surface area and different shades of roughness were generated. Carriers were characterized with respect to particle size, shape and surface topography. The applicability, advantages and disadvantages as well as the benefits of combining several techniques of surface characterization including atomic force microscopy (AFM) will be discussed.

## 2. Materials and methods

### 2.1. Materials

Glass Beads in the size range of 400 μm to 600 μm ($X_{50}$ = 537.3 ± 7.1 μm) were kindly provided by SiLibeads® (SiLibeads® Glass Beads Type S, Sigmund Lindner GmbH, Warmensteinach/Germany). Sodium hydroxide, used for the cleaning procedure was purchased from Carl Roth GmbH + Co. KG, Karlsruhe/Germany. Glass slides (Standard-Objekttraeger, Carl Roth GmbH + Co. KG) as well as ammonium hydroxide, sulphuric acid and hydrogen peroxide, all three chemicals were also used for the cleaning procedure, were purchased from Lactan Chemikalien und Laborgeraete Vertriebsgesellschaft m.b.H & Co. KG, Graz/Austria. Tungsten carbide was provided by Wolfram Bergbau und Huetten AG, St. Martin i.S./Austria and quartz was obtained from Quarzwerke Austria GmbH, Melk/Austria.

### 2.2. Sample preparation

Prior to use, the glass beads were cleaned with Piranha Solution (3:7 $H_2O$:$H_2SO_4$) followed by a standard clean (1:1:5 $H_2O_2$:$NH_4OH$:$H_2O$) and stored in a desiccator over silica gel.

Physical surface modification of glass beads was carried out by friction and impaction in a ball mill (Ball Mill S2, Retsch, Haan/Germany). To get surfaces with different shades of roughness, grinding materials with different Mohs hardness were chosen and glass beads were processed for 8 h and 4 h at 424 rpm. The grinding materials used were tungsten carbide (TC) and quartz (Q) (Table 1). The soda lime glass beads used have a hardness of about 6 on the Mohs scale, so the both grinding materials are harder than glass. The ratio of grinding material to glass beads in the milling chamber was 1:1 (V/V). After grinding the grinding material was separated from the glass beads by sieving on a 250 μm sieve. Then the glass beads were washed with purified water until the supernatant was clean and free of residue of the grinding material (at least 5 times). Finally, the physically treated glass beads were washed again with piranha solution to make sure that all adherent impurities of the grinding procedure had been removed.

### 2.3. Particle surface investigation

Untreated and physically modified glass beads were examined using a scanning electron microscope (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen/Germany) operating at 5 kV. The glass beads had been sputtered with gold–palladium prior to analysis.

### 2.4. Particle size distribution

Due to the large size of the glass beads, the number of glass beads seen by the laser beam would have been too low to get a sufficient intensity of the diffraction patterns with the equipment

**Table 1**
Specifications of the grinding materials used.

| Material | Mohs hardness | $X_{50}$ (μm) |
|---|---|---|
| Quartz | 7 | 32.17 |
| Tungsten carbide | 9.5 | 23.58 |