CHARACTERIZATION OF PHYSICALLY MODIFIED GLASS BEADS AS POTENTIAL MODEL CARRIERS IN DPIS

Contributed by:
Sarah Zellnitza, Jakob Dominik Redlinger-Pohnq, Nora Anne Urbanetz | Research Center Pharmaceutical Engineering GmbH, Graz/Austria

Introduction

Dry Powder Inhalers (DPIs) are medical devices used for pulmonary drug delivery. The formulations used in DPIs typically consist of adhesive mixtures of the drug and a carrier. In order to reach the tiny airways of the deep lung the drug particles have to exhibit an aerodynamic diameter of 1 µm to 5 µm. Particles of this size are rather cohesive and show poor flow properties and thus poor dosing [1]. That is why carrier based formulations, where the drug is attached to the surface of coarser carrier particles (50 µm – 200 µm) of adequate flowability, have been invented.

Interparticle interactions between the drug and d the carrier play a crucial role in carrier-based dry powder inhalers (DPIs). It is important, that they are on the one hand high enough that the drug adheres to the carrier ensuring uniform dosing and on the other hand low enough that drug detachment during inhalation is guaranteed. From literature we can take that interparticle interactions are largely affected by the carrier surface topography [1]. Glass beads were chosen as model carriers because various prospects of chemical and physical surface modification may be applied without affecting other factors that also impact interparticle interactions like particle size and shape of the glass beads.

In the present work the impact of physical surface treatment by friction and impaction in a ball mill on glass beads is analyzed. By treating the glass beads with small hard grinding materials, very fine surface roughnesses that are only visible at large magnifications could be introduced (Fig. 1). As the introduction of surface roughnesses should also lead to an increase in the surface area the specific surface area of the glass beads was chosen as a parameter to quantify the changes.

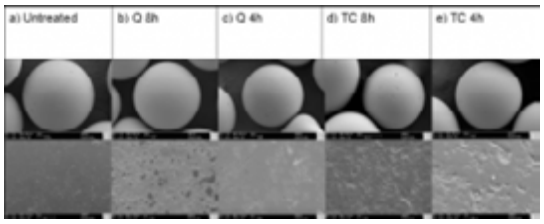

Fig. 1 SEM pictures of a) untreated and b), c), d), e) physically modified glass beads

Materials

Glass Beads (SiLibeads® Glass Beads type S) were used in the size range of 400 µm to 600 µm.The grinding materials used were tungsten carbide (TC) (x50=25 µm; Mohs hardness 9.5) and quartz (Q) (x50=32 µm; Mohs hardness 7). By comparison soda lime glass beads have a hardness of about 6 on the Mohs scale. The Mohs scale of hardness is a common means to rank minerals according to hardness and ranges from a value of 1 for talc to a value of 10 for diamond. Mohs hardness refers to the ability of the material to resist abrasion or scratching and is named after the German mineralogist Friedrich Mohs (1773-1839). Tungsten carbide was provided from Wolfram Bergbau und Huetten AG, St. Martin i.S./Austria and quartz was obtained from Quarzwerke Austria GmbH, Melk/Austria.

Preparation

Surface modification of glass beads was performed mechanically by friction and impaction in a ball mill (Ball Mill S2, Retsch, Haan/Germany). Glass beads were processed for 4 hours and 8 hours with quartz and tungsten carbide powder at 424 rpm. The ratio of grinding material and glass beads was 1:1 (V/V). After treatment glass beads were washed several times with deionised water and dried in an oven at 150 °C for 48 hours. Samples were stored in a desiccator prior to analysis.

Prior to the analysis samples were prepared by degassing with vacuum (0.05 mbar) at 100 °C for at least 4 hours.

Analysis

First analyses were made with nitrogen as adsorber gas, but as the specific surface area of glass beads of the size mentioned above is rather small and no satisfactory results could be obtained, further analyses have been carried out with krypton as adsorber gas. The sample tubes were filled to the maximum with glass beads to compensate for the small specific surface areas of the glass beads and to increase the absolute surface area. Consequently, the average sample mass was about 12 g glass beads. The analyses were carried out with a Tristar II surface area and porosity analyzer (Micromeritics Instrument Company, Norcross/U.S.A.). A 7-point analysis was made between 0.07 and 0.25 relative pressure and the specific surface area was calculated according to the Brunauer-Emmet-Teller (BET) equation. To evaluate the results of our measurements and to make sure that the instrument is capable to measure such small surface areas accurately, the Micromeritics Reference Material Alumina (Part. Nr. 004-16816-00) was weighed in, in such a small amount that the absolute surface area was in the range of the absolute surface area measured for the glass beads. By reducing the sample mass of the standard to about 0.5 g an absolute surface area of 0.105 m² was reached which is comparable to the absolute surfaces measured for the glass beads that were in the size range of 0.09 to 0.2 m². Despite of the small sample size of the standard the measurements still gave a specific surface area of 0.24 ± 0.06 m2/g (mean, n=3 ± SD) which is perfectly fine within the specified range (0.28 ± 0.03 m²/g). Figure 2 shows an example of one of the Alumina standard BET surface area plots. In conclusion it could be shown that the instrument is capable to provide feasible results even below the measuring range specified by the manufacturer.

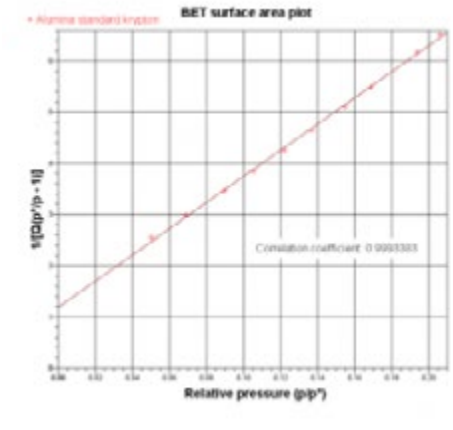

Fig. 2 BET surface area plot of Alumina standard analysed with krypton (10 point analysis between 0.05 and 0.025 relative pressure, weighed portion 0.5488 g)

Data

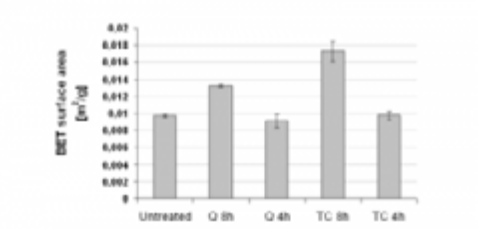

Fig. 3 Specific surface are of untreated and physical modified glass beads (mean of n=3 ± SD)

Figure 3 shows the results of the specific surface area measurements of untreated and physically modified glass beads. Glass beads treated with tungsten carbide for 8 hours exhibit the largest surface area and glass beads treated with quartz for 4 hours the lowest. Treating with quartz for 8 hours and treating with tungsten carbide for 4 hours lead to specific surface areas in between. Actually, the treatment with tungsten carbide for 4 hours leads to a lower surface area than the treatment with tungsten carbide for 8 hours and grinding with quartz for 8 hours leads to a higher specific surface area than grinding with quartz for 4 hours. The results are well in accordance with the hardness of the grinding materials and the processing time and as we would have expected from the SEM images (Fig. 1).

Concluding we can say that gas adsorption has been proved to be a suitable tool to quantify changes in the surface topography/roughness of glass beads even below the measuring range specified by the manufacturer. The measured surface areas are well in accordance with the hardness of the grinding materials, the processing time and the SEM images. By reducing the sample mass of the standard it could be demonstrated that the very small surface areas measured are accurate.

Acknowledgments:

This work is funded by the DFG (German Research Foundation) within the priority program “SPP 1486 – Particles in Contact”.

References:

[1] M. Lohrmann, Adhaesionskraefte in interaktiven Mischungen für Pulverinhalatoren, PhD Thesis, Heinrich Heine University Duesseldorf, 2005.