A deeper insight into the impact of chemical surface properties on inhalation performance

Niklas Renner[1], Hartwig Steckel[2], Nora A. Urbanetz[3] & Regina Scherließ[1]

[1]Department of Pharmaceutics and Biopharmaceutics, Kiel University, Grasweg 9a, 24118 Kiel, Germany [2]Deva Holding A.S., Istanbul, Turkey; [3]Daiichi Sankyo, Tokyo, Japan

Summary

Glass beads (GBs) are ideal to be used as model carriers in dry powder inhalers as they can be selectively surface modified without altering other physico-chemical properties. In this study, GBs in the size range of 400-600 µm were silanised with agents varying in their functional groups thus conferring a broad range of hydrophobicity to the carrier surface, which was determined via contact angle (CA) measurements. Additionally the surface energy (SE) of the carrier particles was measured. Modified and untreated GBs were blended with spray dried budesonide (BUD), serving as a hydrophobic model drug to form interactive mixtures for inhalation. This study expands knowledge gained from the previous study by correlating aerodynamic performance and drug loading to carrier surface characteristics. On the one hand, surface modification had a substantial effect on the actual surface coverage (ASC) as it showed a direct positive correlation to the measured CA. On the other hand, aerodynamic performance was altered by the chemical surface properties of the carrier as a high degree of hydrophilicity (low CA) led to the highest fine particle fraction (FPF). The SEs of not only the carrier but also the API proved to have an impact on both output parameters.

Introduction

Drug delivery by inhalation is distinctively influenced by interparticle forces between carrier and active pharmaceutical ingredient (API) [1]. Those forces are governed by various factors concerning the carrier including particle size [2] and surface topography [3]. The authors have already presented the effect of drug loading on aerodynamic performance using modified GBs [4]. The present study extends previous investigations in order to provide a profound understanding of how carrier surface characteristics influence aerodynamic performance. Therefore, GBs which have been proven to be suitable as model carriers were subjected to a treatment with different silanes to provide a broad range of hydrophobicity. BUD was selected as hydrophobic model API. Since the respirable fraction has been shown to be drug loading dependent and, in addition, the ASC varied with carrier surface modification, the aerodynamic performance of blends containing different modified glass beads cannot be directly compared amongst each other in an appropriate manner. To overcome this issue, blends with three different theoretical surface coverages were prepared for every type of GB and investigated via impaction analysis. Based on data gained from these trials and ASCs, data was normalized by calculating the resulting FPF at a defined ASC of 30 %. Those results can subsequently be correlated to carrier surface characteristics.

Experimental methods

Materials

Crystalline budesonide was purchased from Minakem SAS, Dunkerque, France. Glass beads (SiLibeads® Type S) in the size range of 400-600 µm were kindly provided by Sigmund Lindner GmbH, Warmensteinach. Trimethoxy(3,3,3-trifluoropropyl)silane (FPTS), Chloro(methyl)diphenylsilane (CDPMS) and Chlorotriphenylsilane (TPCS) were purchased from Sigma Aldrich, St. Louis, USA.

Spray drying

Budesonide (BUD) was dissolved in methylene chloride and processed using a Büchi Mini Spray Dryer B290 (Büchi Labortechnik AG, Switzerland) equipped with a high performance cyclone and a Büchi B295 Inert Loop as published previously [4].

Silanisation of glass bead surfaces

Prior to the actual silanisation, the GBs were pretreated with Piranha solution (H_2SO_4:H_2O_2 3:1) to assure a comparable cleanness of the surfaces. GBs were then treated with an ethanolic solution of the respective silane for 30 min. After incubation, they were filtered and rinsed several times with purified water to wash off residual, unreacted amounts of the silane.

Determination of contact angle and surface energy

Contact angle (CA) measurements were conducted at room temperature with an OCA 20 contact angle meter (DataPhysics Instruments GmbH, Filderstadt, Germany). The instrument was coupled to a USB CCD-camera. Inverse gas chromatography (iGC) was used to determine the SE. Samples were filled into a commercially available glass pipe of 4 mm diameter and analysed with an SMS Inverse Gas Chromatograph (Surface Measurement Systems, London, UK).

Preparation of API/carrier blends

Interactive mixtures were produced for calculated surface coverages of 25 %, 50 % and 100 % according to Zellnitz *et al*. [5]. In brief, 15 g of glass beads and the calculated quantity of BUD were weighed in a stainless steel mixing vessel via the double sandwich method. The blending was performed with a Turbula Blender T2C (Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland) for 30 min at 20 rpm. Only homogeneous blends (RSD of blends homogeneity <5%) were used for further experiments.

Aerodynamic assessment

The performance of interactive mixtures was evaluated based on impaction analysis using the Next Generation Pharmaceutical Impactor (NGI) (Copley Scientific, Nottingham, United Kingdom) described as Apparatus E in the European Pharmacopoeia 8.0 and the Cyclohaler® as inhalation device with a fixed flow rate of 100 L/min. 250 mg of the respective blends were filled into hard gelatin capsules of size 3 (Capsugel, Colmar, France) manually using a spatula. For blends with a calculated coverage of 50 % and 100 % the content of three capsules was released in one run, while for blends with 25 % coverage 5 capsules were used in order to ensure sufficient drug for quantification. All NGI experiments were performed in triplicate. Gained data was evaluated using the CITDAS software 3.1 (Copley Scientific, Nottingham, United Kingdom). All trials were conducted in a conditioned environment (20 °C, 35 %RH).

HPLC analysis

Budesonide quantification was done by HPLC on a Waters 600 (Waters Corporation, Milford, USA) and a LiChrospher® RP-18 column (Merck KGaA, Darmstadt, Germany). The mobile phase consisted of 75% (v/v) methanol and 25% (v/v) purified water. The flow rate and column temperature were set to 0.8 ml/min and 20°C, respectively. A sample volume of 100 µl was injected and double determination was conducted. The peaks were detected at 220 nm. Prior to sample analysis a calibration of seven points was created confirming linearity in the range of 0.5 µg/ml to 100 µg/ml.

Determination of actual surface coverage (ASC)

The actual mass ratio of budesonide and glass beads was quantified via HPLC. By comparing these results to the mass ratio for the calculated surface coverages, the ASC could be determined.

Normalisation of FPF

As already mentioned, the theoretical FPF at 30 % ASC was determined for the different GBs. This was done by plotting the FPF against its corresponding ASC for every type of glass bead. Afterwards the resulting FPF was determined with the help of a regression line.

Results and Discussion

Spray drying produced spherical API particles with a median particle size (x50) of 3.1 µm (x10=0.8 µm; x90=7.8 µm). Data obtained from X-ray Powder Diffraction showed an amorphous state for the utilised batch and its stability at 20 °C/35 %rH was proven by Dynamic Vapor Sorption (data not shown). The silanisation process of GBs created surfaces of varying hydrophobicity as illustrated by the respective contact angle. The selected GBs and their corresponding contact angle can be taken from Fig. 1 (left).

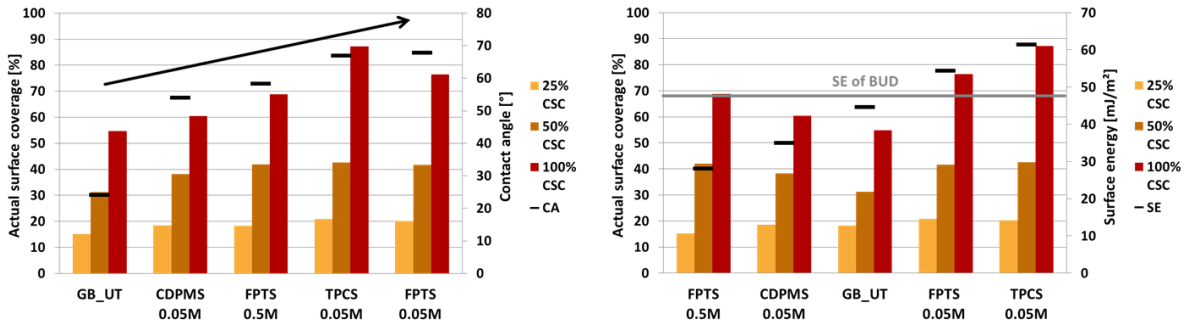

Figure 1 - Actual surface coverages for calculated coverages of 100 %, 50 % and 25 % plotted against contact angle (left) and surface energy (right)

Influence of chemical properties on drug loading

Fig. 1 also illustrates the dependence of actual (effective) surface coverage (ASC) on contact angle (left) and dispersive surface energy (right). Here, the ASC is correlated to the CA in positive manner, as indicated by the ascending arrow. This observation is conclusive in terms of chemical properties of carrier and the hydrophobic API. The relationship between coverage and SE appears prima facie to be non-existent. Including the SE of BUD, a large difference between SEs of carrier and API seems to be favourable to reach high drug loading. While blends prepared with TPCS 0.05M exhibited an ASC of 87.3 %, GB_UT only gained 54.8 %. These findings are also supported by SEM micrographs (Fig. 2). Another study which employed formoterol fumarate as API showed results contrary to those findings. Here, a small discrepancy between SEs of the two components was necessary to obtain optimal drug loading displaying the relevance of physico-chemical nature of the API (data not shown). This is under further investigation.

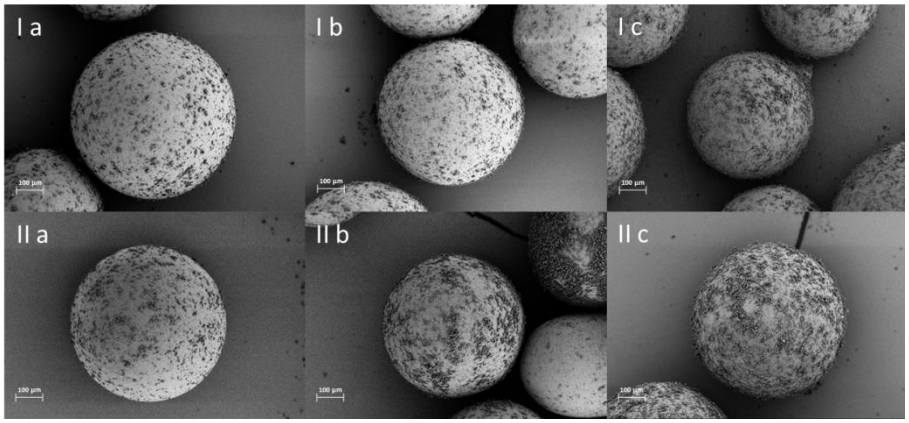

Figure 2 - SEM photographs of blends containing BUD and (I) untreated glass beads or (II) glass beads modified with TPCS 0.05M with different surface coverages of 25 % (a), 50 % (b) and 100 % (c)

Aerodynamic assessment

Fig. 3 (left) displays the effect of CA on inhalation performance, where the FPF decreased with increasing CA illustrated by the descending arrow. Here again, chemical properties provide a logical explanation. The pronounced hydrophilicity of GB_UT facilitates drug detachment and consequently leads to the highest FPF, while with increasing contact angle (increasing hydrophobicity) attractive forces between GBs and BUD are extended. This leads to the lowest respirable fraction for the most hydrophobic carriers (FPTS 0.05M). As seen in Fig. 3 (right) similarity in SEs of carrier and budesonide as API obviously benefits aerodynamic performance as it is the case for GB_UT.

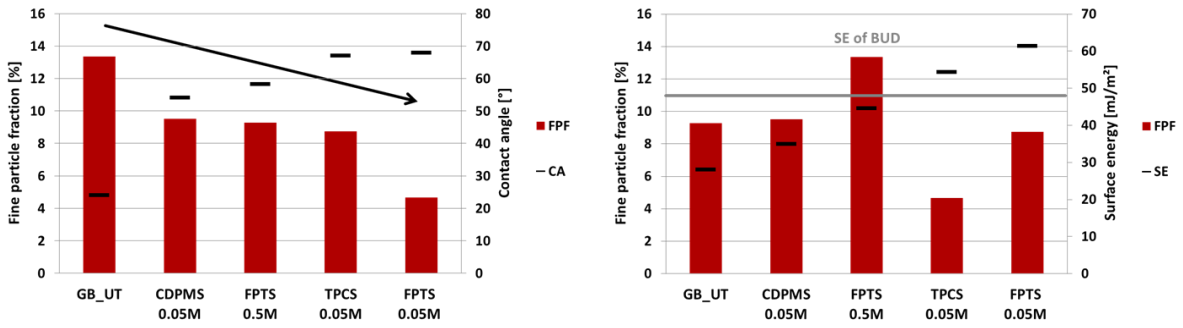

Figure 3 - Resulting FPFs at 30% ASC plotted against CA (left) and SE (right)

Conclusion

Silanisation proved to be a suitable technique to alter chemical surface properties of the model carrier glass beads as it was possible to obtain varying contact angles and dispersive surface energies. Both factors have a substantial effect not only on the effective drug loading but also on aerodynamic performance. While the contact angle is correlated in a positive and negative way directly to ASC and FPF, respectively, the influence of SE has shown to be more complex. Here, the relation between SEs of API and carrier seems to be more important than the absolute values.

Acknowledgements

The authors would like to thank the DFG for funding this project within the priority program SPP 1486 “Particles in contact” and Ann-Kathrin Muhs for her technical support. The authors also want to express their gratitude towards Zinaida Todorova from Otto-von-Guericke University Magdeburg for conducting the silanisation process step.

References

[1] Kou X, Chan L W, Steckel H, Heng P: *Physico-chemical aspects of lactose for inhalation,* Adv Drug Deliv Rev 2012; 64: pp 220-232.

[2] Steckel H, Mueller B W: *In vitro evaluation of dry powder inhalers II: influence of carrier particle size and concentration on in vitro deposition*, Int J Pharm 1997; 154: pp 31-37.

[3] Zeng X M , Martin G P, Marriott C, Pritchard J:.*The influence of carrier morphology on drug delivery by dry powder inhalers*, Int J Pharm 2000; 200: pp 93–106.

[4] Renner N, Scherließ R, Steckel H*: Modified glass beads as model carriers to understand the performance of interactive powder blends* (Abstract). Presented at: *Drug deliver to the lungs 26,Edinburgh*, Scotland, December 9-11, 2015; J Aerosol Med.

[5] Zellnitz S, Schroettner H, Urbanetz N A: *Influence of surface characteristics of modified glass beads as model carriers in dry powder inhalers (DPIs) on the aerosolization performance*, Drug Dev Ind Pharm 2015; 41: pp1710-1717