Carrier-based Dry Powder Inhalation Part II: Impact of carrier material and API processing on the inter-particulate surface interactions in adhesive mixtures for inhalation

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Summary

The aim of this work is to understand the impact of carrier material and API processing on the preparation of adhesive mixtures for inhalation. Additionally, a surface phenomenon, that was observed in a prior study where spray dried salbutamol sulphate seemed to fuse with a specific mannitol carrier surfaces, is investigated further. Therefore, mixtures with two different mannitol carriers and spray dried and micronized salbutamol sulphate as model active pharmaceutical ingredient (API) were prepared. To evaluate the morphology of the different adhesive mixtures SEM images were taken and the air permeability was determined as parameter to detect changed in the powder mixtures resistance to airflow.

From the results, it can be assumed that the observed surface phenomenon is specific for P160C and spray dried salbutamol sulphate. When using micronized salbutamol sulphate no fusion of API and carrier surface occurred. Moreover, also when using a different type of mannitol (Pearlitol 300DC) no fusion occurred.

Introduction

API (active pharmaceutical ingredient) particles intended to target the tiny airways of the deep lung in dry powder inhalers (DPIs) must exhibit an aerodynamic diameter of 1 µm - 5 µm. Therefore, a common (carrier-based) DPI formulation consists of API micro-particles adhered on to the surface of larger excipients particles (50-200 µm) to prevent agglomeration of fine API particles, to improve powder flowability and processability as well as aerosolization during delivery [1]. The most common material used as carrier in majority of commercial carrier-based DPI product is lactose. However, some demerits exist that are inherent to lactose such as potential Maillard reactions with APIs with primary amino groups , poor drug loading capacity, (partial) amorphization/solid-state transitions, variable surface morphology etc.[2].
Mannitol is one of the potential alternative DPI carriers to lactose with advantages of being non-reducing sugar, weaker amorphization tendency and existing stable at anhydrous crystalline form. Our previous work investigated the effect of carrier material, carrier surface processing and capsule filling on the in vitro aerosolization performance. We noticed then that adhesive mixtures of Pearlitol 160C and spray dried salbutamol sulphate showed hardly any API on the surface of the carrier particles although the mixing homogeneity indicated that the API is distributed well on the carrier. It seemed that the mannitol surface appeared somehow apparently “coated” with the fused API on to the carrier surface [3]. Within this study, the previously observed unique surface phenomenon were further investigated including salbutamol sulphate micro-particles prepared by spray drying and micronization and with two different grades of mannitol.

Materials

Mannitol samples (Pearlitol® 300DC and Pearlitol 160C) were kindly provided by Roquette Frères (Lestrem, France). Salbutamol sulfate (USP25 quality) was purchased from Selectchemie (Zürich, Switzerland).

Methods

Inhalable salbutamol sulphate particles were prepared on a Nano Spray Dryer B-90 (Büchi Labortechnik AG, Flawil, Switzerland) equipped with the long version of the drying chamber and piezoelectrically driven vibrating mesh as the atomizer spray head. Aqueous salbutamol sulfate solutions used for spray drying were prepared with purified water (TKA Micro Pure UV ultra-pure water system, TKA™ water purification systems, Niederelbert, Germany) equipped with a capsule filter (0.2 µm).

To form particles in the size range of 1 µm - 5 µm (characteristic diameters: x10=0.45 µm, x50=3.07 µm and x90=6.73 µm). a spray head mesh of 7 µm was chosen and a feed concentration of 7.5%. The flow rate was set to 100 L/min and the spraying intensity was set to 30 % [4].

Additionally, salbutamol sulphate was micronized using an air jet mill 50 AS (Hosokawa Alpine, Augsburg, Germany). The injection pressure was 3.0 bar and the milling pressure 2.0 bar. The micronized material showed a mean particle size of 1.84 µm (characteristic diameters: x10 = 0.49 µm, x50 = 1.84 µm, x90 = 4.76 µm).

Particle size analysis of spray dried and micronized salbutamol sulphate particles was carried out using a HELOS laser diffraction system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a RODOS dry powder dispersing system (Sympatec, Clausthal-Zellerfeld, Germany) at an air pressure of 3 bar. Particle size calculations based on the Fraunhofer theory.

The spray dried and micronized API as well as the quality of the adhesive mixtures was examined using a scanning electron microscope (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen/Germany) operating at 5kV. Samples were gold palladium sputtered before the measurement.

Adhesive mixtures of the different mannitol carriers with spray dried or micronized salbutamol sulphate particles were prepared in a Turbula blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland). For this, 148.5g of mannitol and 1.5g of micronized or spray dried salbutamol sulphate were weighed into stainless steel mixing vessels (diameter: 3.2 cm, height: 3,4 cm; filling volume approximately 40%) using the sandwich method. The vessel was then fixed in the Turbula blender and mixed for 60 min at 60 rpm.

Air permeability measures an extent to which a material can transmit air through its bulk powder bed and is expressed by the air pressure drop (PD) across thebed. The test was performed with pressurized dry air (2×10-3 m/s air velocity) with the FT4 powder rheometer (Freeman Technology, UK) applying a range of normal stress on the DPI blends.

Results and Discussion

Figure 1 shows SEM images of the spray dried (Fig.1a) and micronized salbutamol (Fig. 1b) particles. SEM images show that both techniques were able to produce particles that have suitable size for inhalation but with very different shape and morphology. Spray dried particles are spherical, whereas micronized particles are needle shaped. Moreover, spray dried particles are amorphous while micronized particles were largely crystalline [4]. The mean particle size (x50) determined via laser diffraction for spray dried particles is 3.07 µm and for micronized particles 1.84 µm.

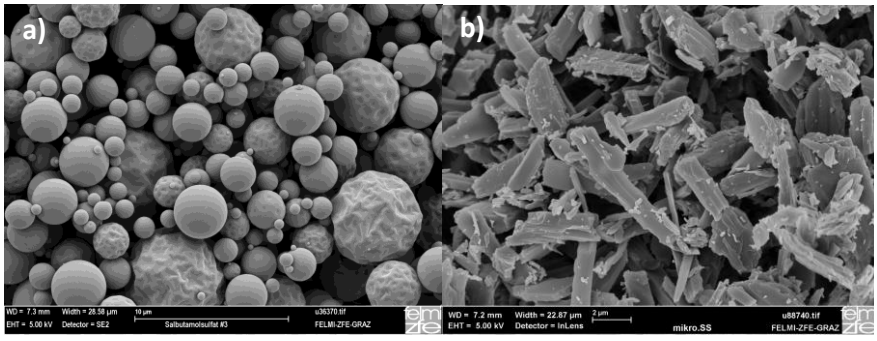

Figure 1 SEM images of micronized and spray dried salbutamol sulphate particles.

Adhesive mixtures were prepared of the spray dried and micronized material with two different standard mannitol carrier particles, P160C and P300DC. SEM images of P160C with spray dried salbutamol sulphate (Fig. 2a) show hardly any API on the surface of the carrier particles. This phenomenon was reproduced as the observation in our previous work. By contrast, spray dried salbutamol particles can be clearly seen on the surface of P300DC particles after mixing (Fig. 2c). Further, SEM images also show the presence of micronized salbutamol sulpahte particles on the carrier surfaces in adhesive mixtures with either P160C or P300DC.

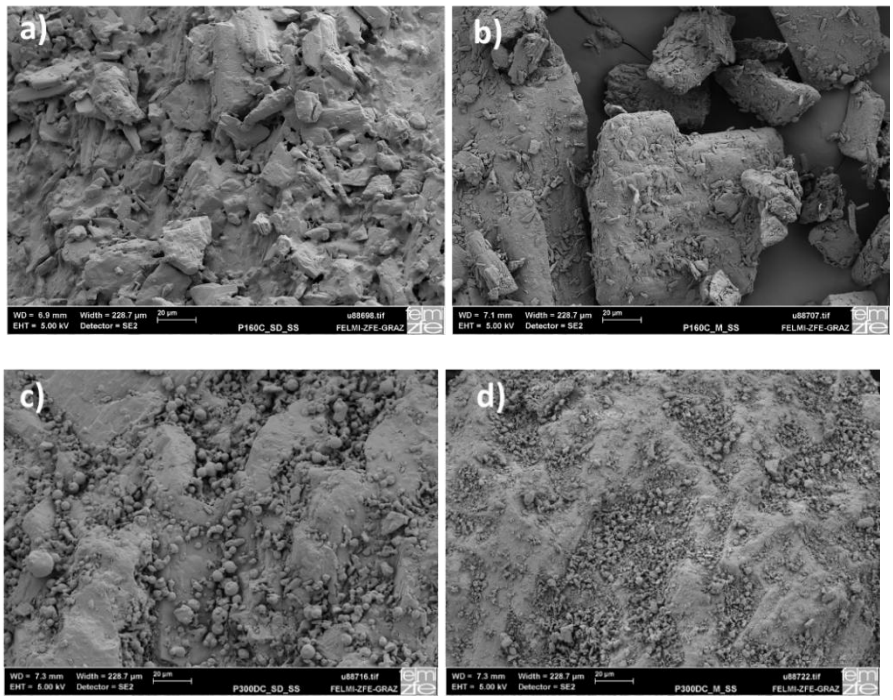

Fig. 2 SEM images of adhesive mixtures containing P160C with a) spray dried and b) micronized salbutamol sulphate particles and containing P300DC with c) spray dried and d) micronized salbutamol sulphate particles.

Looking at the surface of P160C particles blended with spray dried and micronized salbutamol sulphate again at higher magnifications (Fig. 3a,b), it seems that the surface of P160C appeared apparently “coated” after blending with spray dried API, wherein API particles seemed fused on to the carrier surface. However, in case of micronized salbutamol sulphate, individual micronized particles can be visualized on the surface of P160C particles at high magnification.

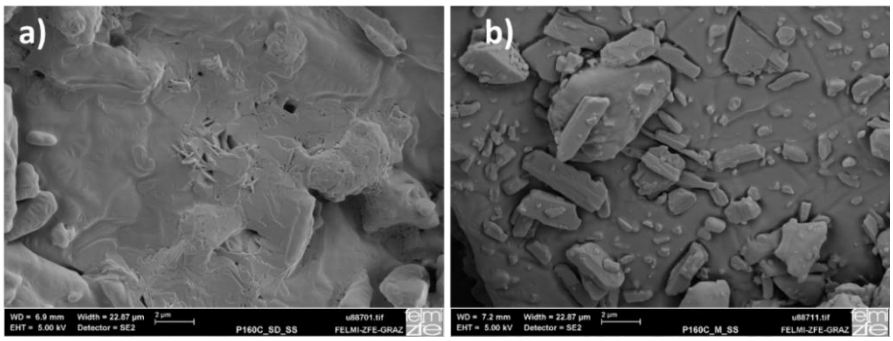

Figure 3: SEM images of adhesive mixtures containing P160C and a) spray dried and b) micronized salbutamol sulphate particles.

In our previous study, blends containing P160C and spray dried salbutamol sulphate showed rather different the different air permeability behavior compared to blends containing lactose and surface modified lactose and mannitol. It seemed that the fusion of API and/or fines onto the carrier surface led to a higher resistance for the air throughput. To further investigate this hypothesis, the air permeability was measured for the different blends used in the present work.

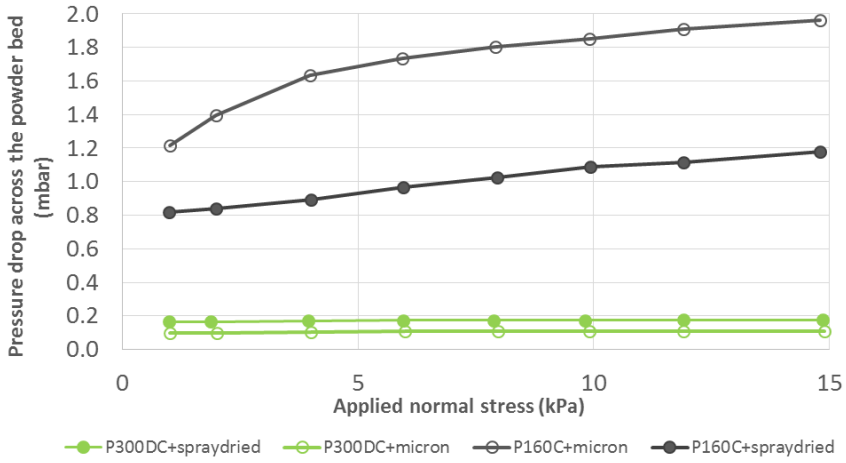

Figure 4: Air permeability of the adhesive mixtures

Fig. 4 displays the permeability of the different adhesive mixtures. Permeability is a measure of the powder's resistance to air flow and a high pressure drop indicates low air permeability. High air permeability is obtained for large particles, as inter-particular spaces are larger and inter-particulate interactions are relatively weaker, reducing the pressure drop as less boundary layer area is generated per unit volume. Fine particles fill up residual spaces between the larger carrier particles and thereby increase the resistance to air flow upon compression, therefore relatively higher fraction of fines in a powder decreases air permeability through the powder bed [5].

The lower values of pressure drop across a range of values of applied normal stress for the blends containing P300DC and spray dried or micronized API implied that air permeability through these blends is relatively higher compared to blends containing P160C. Moreover, there is no noticeable difference when spray dried or micronized API is used in the blend and throughout variable normal stress. Both differently prepared API particles are distributed homogenously, as per the observation of individual non/agglomerated API particles on the carrier surface (Fig. 2c, 2d), and therefore contribute to the high air permeability in P300DC containing blend. In contrary, the permeability for blends containing P160C was relatively lower and for these blends a difference between micronized and spray dried API could be observed. The lower air permeability for P160C could be owing to the smaller particle size of P160C carrier particles. For P160C and spray dried salbutamol sulphate, the air permeability is quite low (with the highest values of pressure drop), like in our previous study. This might be due to the observed surface phenomenon.

Conclusion and Outlook

Through this study, it was found that the observed surface fusion-like phenomenon is specific for P160C and spray dried (amorphous) salbutamol sulphate. When using micronized API (which is largely crystalline), no fusion of API and carrier surface occurred with both of mannitol grades used.

Moreover, this study reveals an exciting observation that selection of suitable mannitol grade enable an efficient surface adherence of spray dried particles of salbutamol sulphate-like API. Our ongoing work is focused on further elucidation of the observed interesting finding on the carrier specific surface interaction behaviour of API.

The aim of further work will also be towards the in vitro determination of the fine particle fraction (FPF) for the different mixtures, with the special focus on the spray dried API and different mannitol system. Additionally, more different mannitol types will be evaluated in blends with micronized and spray dried salbutamol sulphate. The obtained data are highly useful to improve the understanding of the surface properties of mannitol based DPI and performance therefrom.

References

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