Impact of particle engineering on the processability and aerosolization performance of DPI formulations

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Summary

Active pharmaceutical ingredient (API) particles administered via dry powder inhalers (DPIs) must exhibit an aerodynamic diameter of 1µm - 5µm. Particles of such a small size are rather cohesive and show poor flow properties. This is challenging for the dose uniformity, as a good flowing powder is required to guarantee uniform doses for example during capsule filling or dose metering within a reservoir inhaler. To overcome this problem, carrier based formulations where the small API particles are attached to larger carrier particles with adequate flowability have been invented. A crucial step during inhalation is the detachment of the API from the carrier. Only detached API particles are able to reach the lung. The detachment process is governed by API as well as carrier properties. Therefore, within this study the effect of particle engineering on capsule filling performance represented by capsule fill weight and weight variability and on aerosolization performance represented by the fine particle fraction (FPF) and the emitted dose (ED) were investigated. Inhalation grade lactose was used as carrier material as received and after wet surface processing. Spray dried and jet milled salbutamol sulphate served as model API. Results showed that compared to API engineering carrier engineering had a positive effect on weight variability. Moreover, the use of spray dried API particles overall decreased the FPF. Engineered carrier particles showed improved FPF but only in combination with jet milled API. The highest FPF (≈33%) was obtained for jet milled API in combination with engineered lactose carrier particles.

Introduction

Formulation development for dry powder inhalers (DPIs) is challenging as in order to reach the deep lung active pharmaceutical ingredient (API) particles must exhibit an aerodynamic diameter of 1µm - 5µm. Particles of such a small size are typically rather cohesive and show poor flow properties. This however is challenging during the formulation and dosing process where a good flowing powder is required to guarantee uniform doses for example during capsule filling or dose metering within a reservoir inhaler. To overcome this challenge carrier based formulations where the small API particles are attached to a larger carrier particle (usually 50µm – 200µm) with adequate flowability have been developed. A crucial step during inhalation is the detachment of the API from the carrier. Only detached single API particles are able to reach the lung where they are supposed to cause a therapeutic effect. This detachment process is impacted by API as well as carrier properties and many studies have focused on either carrier or API engineering in order to tailor drug detachment from the carrier [1]. There is a complex interplay between particle engineering, particle properties, their processability and aerodynamic performance. Most studies focus on the effect of particle engineering on the aerodynamic performance but also the effect on processability must not be neglected. Therefore, the present study evaluates the effect of particle engineering on the processability during capsule filling as well as on the aerodynamic performance.

This study presents a follow up study to work that was shown at last year's DDL, where also the influence of carrier surface processing on capsule fill performance and aerosolization performance was analyzed [2]. This study should complement the data already presented by investigating a different carrier engineering technique. The obtained data shall help in a more comprehensive understanding of the interplay between carrier morphology and carrier type, drug detachment and capsule filling efficiency. The final goal would be to collect these data for various different carrier materials to generate a platform technology encompassing a detailed understanding on how different engineering techniques affect particle characteristics and further capsule fill performance and aerodynamic performance. Ideally, this platform should allow the preselection of matching API carrier pairs and process settings based on particle characteristics.

Materials and methods

API engineering

Salbutamol sulphate (SS) (Selectchemie, Zurich, Switzerland) was chosen as a model API in the present study. To generate inhalable sized particles salbutamol sulphate was micronized using spray drying (Nano Spray Dryer B-90 (Buechi Labortechnik AG, Flawil, Switzerland) and jet milling (Spiral Jet Mill 50 AS, Hosokawa Alpine AG, Augsburg, Germany). Spray drying conditions were chosen according to our previous work [3]. Air jet milling was done at an injection pressure of 6 bar and a pressure inside the micronizer chamber of 3 bar.

Carrier engineering

Besides engineered API particles, also engineered carrier particles were used. Carrier engineering was performed through wet surface processing of α-lactose monohydrate, with the intention to on the one hand remove fine particles adhering to the bulk carrier material and on the other hand to modify the carrier surface topography [4].

Preparation of adhesive mixtures

For evaluating the performance of engineered materials, blends of spray dried (SDSS) and jet milled (JMSS) salbutamol with lactose raw material (LAC R) and engineered lactose (LAC E) were prepared. In total four adhesive mixtures with 2% API content were manufactured in a tumble blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland). Mixing parameters were chosen as follows, 60min at 60rpm.

Powder characterization

Both, raw and engineered carrier as well as the differently prepared APIs were extensively characterized. Particle size was measured via laser diffraction (HELOS, Sympatec, Clausthal-Zellerfeld, Germany). Particle morphology was measured via scanning electron microscopy ((SEM), Zeiss Ultra 55, Zeiss, Oberkochen, Germany). Solid state was analyzed via differential scanning calorimetry ((DSC), 204F1 Phoenix®, Netzsch GmbH, Selb, Germany) and small- and wide angle x – ray (SWAXS) scattering (S3 – MICRO camera (formerly Hecus X ray systems, Graz, now Bruker AXS, Karlsruhe, Germany)). Particle characteristics were used to evaluate the effect of processing by comparing the different particulate properties.

For all adhesive mixtures SEM images (SEM, Zeiss Ultra 55, Zeiss, Oberkochen, Germany) were taken to visualize the distribution of API on the carrier surface. Moreover, adhesive mixtures were characterized in terms of flowability. Therefore, bulk density (BD) and tapped density (TD) were determined with a PT-TD200 (Pharma Test Apparatebau AG, Hainburg, Germany) according to a standardized method described in the United States Pharmacopeia (USP 2011). From these results the Carr´s Index or Compressibility Index (CI) was calculated upon the volumes of BD and TD and Houser Ratio (HR) calculated.

Capsule filing

Capsule filling was performed with two different process setting on a dosator nozzle capsule filling machine (Labby, MG2, Bologna, Italy) with a target fill weight of 20mg to 25mg at a filling rate of 2500 capsules per hour (cph).
Setting 1: 3.4mm dosator, 2.5mm dosing chamber, 5mm powder layer
Setting 2: 3.4mm dosator, 2.5mm dosing chamber, 10mm powder layer

Blend uniformity during filling was checked by sampling filled capsules during filling. Therefore 25 filled capsules were collected after 5 and 10 minutes from the beginning of capsule filling. The API content in each capsule was evaluated by dissolved the capsule content in 20ml of buffer (diluted acetic acid solution (pH=3)) and quantifying the salbutamol content using a validated HPLC method. The homogeneity of the mixtures is expressed by the relative standard deviation (RSD) of the mean sample drug content.

Aerodynamic assessment of particles

To assess the impact of API engineering as well as carrier engineering on the in vitro performance, lung deposition experiments were carried out with a next generation impactor (NGI, Copley Scientific, Nottingham, United Kingdom). For each NGI experiment, three capsules were discharged via the Aerolizer®/Cyclohaler® and the salbutamol content in each part of the impactor quantified using a validated HPLC method. For all experiments the emitted dose (ED) and the fine particle fraction (FPF) were calculated based on the specification of the European pharmacopoeia.

Results and discussion

Powder characteristics

API processing significantly affects the final product characteristics. Spray drying resulted in spherical amorphous particles whereas by jet milling crystalline needle shaped particles were generated. Further, the engineered API particles differ in terms of size. (Characteristic diameters of spray dried particles x_{10}=0.45µm, x_{50}=3.07µm and x_{90}=6.73µm, characteristic diameters of jet milled particles: x_{10}=0.52µm, x_{50}=1.99µm and x_{90}=5.03µm).

Carrier engineering via wet surface processing resulted in smoother particles with less fine lactose attached compared to the raw material. This was visualized via SEM images and reflected via particle size measurements by a slightly reduced particle size for the engineered carrier material (Characteristic diameters of the engineered carriers particles: x_{10}=71.4µm, x_{50}=179.04µm and x_{90}=313.93µm; characteristic diameters of the raw material: x_{10}=95.27µm, x_{50}=216.03µm and x_{90}=354.7µm). Moreover, SEM images revealed that wet surface processing introduced shallow cavities on the surface. Solid state analysis revealed that during the wet surface processing the surface was solvated and during drying recrystallized in form of small anhydrous lactose particles [4, 5].

As a measure for the flowability of the different adhesive mixtures, the CI and the HR were evaluated. Results in Figure 1 show that carrier engineering lowered the CI and the HR indicating a better flowability of the mixture. This is true for mixtures of engineered carrier and both spray dried and jet milled API. The use of engineered API in the blend preparation seemed not to affect the flowability of the mixtures what is most likely due to the small amount of API present in the mixtures.

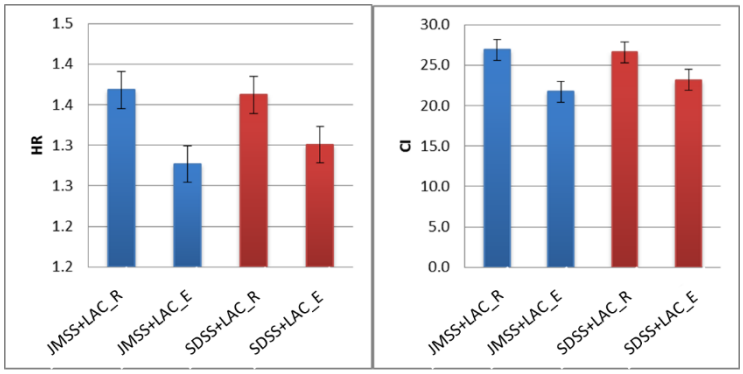

Figure 1. CI and HR for all adhesive mixtures, calculated from bulk and tapped density measurements (n=3)

Processability – Capsule filling performance

Blend uniformity during filling was evaluated after 5 and 10 minutes from the beginning of capsule filling. A decrease in blend uniformity values represents a more homogenous distribution of API within the mixture. Overall results in table 1 show that the blend uniformity is good for all formulations independent of what carrier and API combination is used and what process settings are chosen. Comparing the two different process settings one can see that for settings 2 the blend uniformity improves with increasing capsule filling time. Whereas for process settings 1 this effect is less pronounced. Having a look on the impact of particle engineering, values of mixture homogeneity show a different behavior for jet milled and spray dried blends. The use of engineered carrier shows improved blend uniformity but only when combined with spray dried API. This is true for both process settings and sampling time steps. For the micronized blends the use of engineered lactose seems to reduce the blend uniformity except for a pbh of 10mm after 10 minutes where the blend uniformity improves. These results show that wet surface processing of the lactose carrier leads to more uniform mixtures when formulated with spray dried API.

Table 1. Mixture homogeneity during filling process at different powder bed heights. Samples were taken from 5 to 10 minutes and from 10 to 15 minutes (n=25, RSD from mean drug content)

	Blend uniformity - Setting 1 [%]		Blend uniformity - Setting 2 [%]	
	Min 5-10	**Min 10-15**	**Min 5-10**	**Min 10-15**
JMSS+LAC_R	1.44	0.98	2.96	1.35
JMSS+LAC_E	1.75	1.62	3.80	0.93
SDSS+LAC_R	2.11	1.33	3.90	1.81
SDSS+LAC_E	1.07	0.66	3.32	1.48

For the evaluation of capsule filling performance two parameters were chosen, the target fill weight and the weight variability expressed by the relative standard deviation (RSD). Results in table 2 show that the intended fill weight of 25mg per capsule was achieved for all blends within the given limits of accuracy of a RSD below 5 %. However, when having a closer look on the values, it can be clearly seen that the weight variability is reduced when using engineered lactose particles (lower RSD values). This effect is true for both process settings but more pronounced for settings 1. Moreover, when applying process settings 1 the use of engineered carriers led to higher fill weights compared to raw lactose carriers.

Table 2. Fill weight and fill weight variability (RSD)

	Setting 1 [mg]	RSD [%]	Setting 2 [mg]	RSD [%]
JMSS+LAC_R	19.74	6.57	27.22	2.00
JMSS+LAC_E	24.07	2.37	25.08	1.97
SDSS+LAC_R	20.85	4.19	27.19	2.33
SDSS+LAC_E	24.74	2.21	27.33	2.00

Concluding, carrier engineering had a positive effect on weight variability whereas API engineering seemed not to affect the capsule filling performance. This could be explained by the amount of API that is relatively small in the mixtures. The positive effect of engineered lactose on the capsule filling performance can be related to the increased flowability of adhesive mixtures containing engineered lactose particles (Figure 1).

Assessment of aerodynamic performance

For the evaluation of the performance of the different mixtures, the fine particle fraction (FPF) and the emitted dose (ED) were chosen. Results in table 3 overall show that mixtures comprising of spray dried API and either raw or engineered lactose show much lower FPFs compared to adhesive mixtures containing jet milled API particles. Thus, API engineering has a larger effect on the aerodynamic performance than carrier engineering. The use of engineered lactose particles increase the FPF when using jet milled API in combination with process setting 1 and had no effect at process settings 2. By contrast, when spray dried API is use the FPF decreases for the engineered carrier material. The highest FPF was obtained for jet milled API in combination with engineered lactose particles at process settings 1, indicating this as most favorable API-carrier combination within the presents study. For both process settings the same trends for FPF can be observed, so the different process settings do not affect the aerosolization performance.

The ED is within the same range for all adhesive mixtures. Although there is a slight tendency that the use of spray dried API increases the ED, especially at process settings 1.

Table 3. In Vitro performance: Fine particle fraction (FPF) and Emitted dose (ED)

Samples	Setting 1		Setting 2	
	FPF [%]	ED [µg]	FPF [%]	ED [µg]
JMSS+LAC_R	19.20	829.88	22.41	1131.95
JMSS+LAC_E	32.53	939.91	22.63	1077.56
SDSS+LAC_R	6.49	1035.02	5.07	1114.91
SDSS+LAC_E	2.39	1261.05	3.35	1162.72

Concluding, results showed that drug detachment and aerodynamic performance is governed by the API particles used. Although carrier engineering positively affected capsule filling no benefit on the aerosolization performance could be observed. This could be explained by particle characteristics that were more distinct for the differently prepared API particles than for raw and engineered carrier particles. API engineering resulted in particles with different size shape and solid-state whereas carrier engineering manly changed surface topography.

Conclusions

The obtained data are highly useful, to improve the understanding of the relationship between carrier morphology on capsule filling efficiency and aerosolization performance. Moreover, these data help to approach the platform technology with the final goal to preselect matching API carrier pairs and process settings based on particle characteristics.

References

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