The influence of intrinsic and extrinsic lactose fines on the performance of dry powder inhaler formulations

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Summary

It is a well-known formulation concept to increase the fine particle fraction (FPF) of dry powder inhalers (DPIs) by the addition of lactose fines. Usually during a first mixing step lactose carrier particles and fines are blended. In a second mixing step the API is added and ternary mixtures between the lactose carrier, the lactose fines and the API form. As all commercially available lactose fines are produced by milling little is known about the influence of the origin of the fines and hence the physico-chemical properties of the fines on the DPI performance. For this reason the aim of this work was to study the influence of intrinsic fines, which were prepared during the crystallization of the carrier material, and extrinsic milled fines, which were added to a carrier with a reduced fines content in a separate mixing step, on the performance of a DPI formulation. Adhesive mixtures with a hydrophilic (salbutamol sulfate) and a lipophilic (budesonide) API and three different carrier combinations (lactose RF "reduced fines", lactose IF "intrinsic fines" and lactose EF "extrinsic fines") were prepared and further analyzed.

Only the presence of externally added milled fines increased the FPF. The presence of intrinisic fines did not improve the FPF. The physico-chemical properties of the carrier combinations assessed in this study such as amorphous content and surface energy couldn´t be used to predict the performance of the formulation.

Introduction

In dry powder inhaler formulations usually two different formulation approaches are used. One option is the formation of so-called soft pellets by an intended agglomeration process. The second more widely used approach is the use of a coarse excipient which acts as a carrier for the micronized drug particles [s

1]. As such coarse carriers different sugars and sugar alcohols can be used [2, 3]. The most frequently used carrier is α-lactose-monohydrate.

The addition of fine lactose particles to the coarse carrier material is a well-known approach to increase the inhalable fraction [4]. By pre-blending the coarse carrier with fine lactose particles, cavities and high-energy sites on the carrier surface are saturated, which facilitates drug detachment during inhalation. In addition the formation of agglomerates out of fine lactose and drug particles is assumed to improve the inhalable fraction of dry powder inhaler formulations [4].

As all commercially available lactose fines (x_{50}≤10µm) are produced by milling most of the studies focus on the influence of milled fines on the performance of DPI formulations. However due to the high energy input the physico-chemical properties of milled or micronized lactose grades can differ from grades produced by crystallization (e.g. shape, amorphous content). For this reason the aim of this work is to study the influence of intrinsic and extrinsic fines on the performance of DPI formulations. The intrinsic fines were generated during the crystallization process of the coarse carrier. By changing the crystallization conditions it was possible to reduce the amount of fines. Subsequently milled fines were added to the carrier with reduced fines content (extrinsic fines). Adhesive mixtures with either salbutamol sulfate, as hydrophilic model API, or budesonide, as hydrophobic API, were prepared with all of the three lactose grades (lactose reduced fines (RF), lactose intrinsic fines (IF) and lactose extrinsic fines (EF) and further analyzed.

Materials & methods

Materials: InhaLac® 250, lactose with intrinsic fines ("**lactose IF**"); Lactose with reduced fines named "**lactose RF**"; Lactose with extrinsic fines ("**lactose EF**") was prepared by mixing of lactose RF and InhaLac® 400 (5% w/w), a fine milled inhalation grade lactose, (all lactose grades Meggle Excipients and Technology, Germany). Mixtures were prepared on a Turbula blender T2F (Willy A. Bachofen Maschinenfabrik, Switzerland) at 72 rpm and 30 min using the sandwich method.
Adhesive mixtures: Turbula TC2 blender (Willy A. Bachofen Maschinenfabrik, Switzerland), 72 rpm, 60 minutes, batch size: 100g, double sandwich method, API: 2% w/w. Prior to the preparation of the mixtures the APIs and lactose grades were sieved through a 180 µm sieve. Also during the mixing process the blender was stopped every 15 minutes and the powders were sieved through a 180 µm. Before NGI testing the powder blends were stored at room temperature and 45 % RH for 24 h.

The particle size distribution: HELOS KR laser diffraction system and RODOS/L dry dispersion unit (Sympatec GmbH, Germany), dispersion pressure: 3 bar, R3 lens (lactose grades), R1 lens (APIs)
Bulk and tapped densities measurement according to the European Pharmacopoeia (2.9.34, method 1; Ph. Eur. 8.0) using a SVM 222 (Erweka, Germany).
Specific surface area: nitrogen absorption (2.9.26, Ph. Eur. 8) using a Gemini 2360 (Micromeritics, Germany), degassing of samples for 20 h at room temperature using vacuum, pP/P_0 from 0,05 to 0,3 (11 steps), Brunauer Emmet and Teller equation. Measurement of true density: helium pycnometer (Pycnomatic, Porotec).
Amorphous content: DVS-HT (Surface Measurement Systems Ltd., United Kingdom) by using moisture sorption isotherms. After drying the samples for 20 h the relative humidity was increased stepwise under isothermal conditions at 25°C (3%, 5%, 7.5%, 10%, 15%, 20%, 30%, 40%). Each step was hold until dm/dt was <0.0005% or for a maximum of 27 h. The amorphous content was calculated based on the monolayer capacity by using the linearized form of the Brunauer, Emmet and Teller equation. As at higher partial pressures the measured values varied from the calculated curve progression, only partial pressures up to 0.2 were included. For the external calibration physical mixtures out of crystalline and milled amorpous lactose in different concentrations were used [5].
A**nomeric content**: Bruker Avance III nuclear magnetic resonance spectrometer (Bruker Corporation, USA), measurements under isothermal conditions at 298 K. To avoid mutarotation approximately 3 mg of each sample were dissolved in DMSO-d_6 99.6% immediately before measuring the anomeric content. DMSO-d_5 signal at 2.50 ppm was used as an internal standard.
The powder samples were examined using a Smart SEMTM Supra 55VP **scanning electron microscope** (SEM) (Carl Zeiss AG, Germany) operating at 2-5kV. Powder samples were sputtered with gold prior to examination.
Blend homogeneity: 10 samples of 10 mg were drawn from the powder blends via a spatula- three from the top, four from the center and three from the bottom of the vessel and subsequently analyzed by HPLC. Batches with a CV below 5% were accepted for further testing.
Drug content and homogeneity of the adhesive mixtures and NGI samples was determined using a high-performance liquid chromatography (**HPLC**) system equipped with a 250 mm RP-18 column and a RP-18 pre-column. For the determination of salbutamol sulfate the mobile phase consisted of 15 % methanol and 85 % phosphate buffer (pH 3.0). For budesonide a mixture of 75 % methanol and 25 % bidistilled water was used as mobile phase. Flow rate: 1 mL/min. Either 100 µl (salbutamol sulfate) or 50 µl (budesonide) of the sample were injected per run. Detection was carried out at 224 nm for salbutamol sulfate and at 244 nm for budesonide. Each sample was injected twice. The drug amount was calculated by using an external calibration curve, consisting of 8 solutions of known concentration from 0.5 -100.0 µg/mL.
The aerodynamic assessment of fine particles: (2.9.18., Ph. Eur., 8.0) apparatus E (Next Generation Pharmaceutical Impactor (NGI), Copley Scientific, United Kingdom), cups and the preseparator were coated with a mixture of Brij® 35 (15%), ethanol (51%) and glycerol (34%), flow rate: 80.0 L/min. The solenoid valve of the critical flow controller (TPK, Copley Scientific, United Kingdom) was kept open for three seconds so that 4 l of air were sucked with a vacuum pump (HCP5, Copley Scientific, United Kingdom) through the NGI. An **application system** (stainless steel tube with an inner diameter of 5 mm and a total length of 170 mm) was used to eliminate the influence of a specific device [2]. 10 single doses containing each 10 mg of powder (corresponding to 200 µg API) were weighed into the cavity and released into the NGI by rotating the inner part of the applicator. The amount of drug found in the NGI was determind by HPLC. The fine particle dose (FPD) is calculated as the dose of the active ingredient exhibiting an aerodynamic diameter of < 5 µm. The emitted dose is the amount of the active found in the whole impactor (mouthpiece adaptor, introduction port, preseparator, impaction stages). The fine particle fraction (FPF) is defined as the fine particle dose divided by the emitted dose.

Results & discussion

The particle size distributions (PSDs) of the lactose grades and the APIs are shown in table 1. Lactose IF and lactose EF have a similar x_{10} (10.3±0.3 µm and 9.0±0.2 µm) whereas the x_{10} of lactose RF is larger (19.2±0.3 µm). All of the carrier materials have similar x_{50} and x_{90}.
The amount of fines was derived from the PSD curves as % <4.5 µm. The change in the crystallization process resulted in a lactose with a reduced fines content (lactose RF:<4.5 µm: 3.9±0.1 %). The fines content of lactose IF (<4.5 µm: 5.8±0.2 %) is slightly lower than the one of lactose EF (<4.5 µm: 7.2±0.1 %).

	x_{10} / µm	x_{50} / µm	x_{90} / µm	<4.5 µm / %
Lactose IF	10.3±0.3	49.6±1.2	94.4±2.0	5.8±0.2
Lactose EF	9.0±0.2	54.3±0.1	87.3±0.2	7.2±0.1
Lactose RF	19.2±0.3	55.8±0.5	84.7±1.1	3.9±0.1
Salbutamol sulfate	0.8±0.0	2.4±0.0	5.9±0.3	-
Budesonide	0.5±0.1	1.8±0.0	4.9±0.1	-

Table 1 - Particle size distributions of lactose grades and API particles (mean n=3±SD)

Comparison of the surface areas of the three carriers shows the highest surface area for lactose EF, followed by lactose IF and lactose RF, as with increasing particle size and decreasing amount of fines the surface area decreases (table 2). Interestingly the difference in surface area between lactose EF and lactose IF (0.08 m^2/g) is much larger than that of lactose IF and lactose RF (0.02 m^2/g). This is unexpected as the difference in the amount of fines <4.5 µm is larger for lactose IF and lactose RF (1.9 %) compared to lactose EF and lactose IF (1.4 %).
The anomeric content of all samples is between 96 % and 98 % (table 2). Lactose IF shows the highest content of α-lactose with 97.67±0.21 %. For Lactose RF and Lactose EF a comparable, slightly lower α-lactose content was measured (96.44±0.18 % and 96.59±0.09 %).
For all carrier lactose grades an amorphous content below 1 % was measured (table 2).
Lactose RF has a bulk density of 0.72±0.01 g/mL and a tapped density of 0.82±0.00 g/mL. Similar values were measured for lactose EF (0.71±0.00 g/mL and 0.82±0.00 g/mL). Lactose IF shows a lower bulk and tapped density (0.63±0.00 g/mL and 0.77±0.00 g/mL; table 2).

	Surface area / m^2/g	Bulk density / g/mL	Tapped density / g/mL	Amorphous content / %	Anomeric content / %	Surface energy / mJ/m²
Lactose IF	0.2607	0.63±0.00	0.77±0.00	0.25±0.01	97.67±0.21	45.51±0.83
Lactose EF	0.3382	0.71±0.00	0.82±0.00	0.85±0.05	96.59±0.09	45.52±0.23
Lactose RF	0.2394	0.72±0.01	0.81±0.01	0.80±0.12	96.44±0.18	38.44±0.09

Table 2 - Physical-chemical properties of the lactose grades (surface area: mean n=2; all others: mean n=3±SD)

On the images of the lactose grades it can be seen that the overall particle shape of all three carrier materials is similar (figure 1, upper line). The powders consist of single crystals, which are partly tomahawk-shaped. The images with the larger magnification (figure 1, lower line) reveal the fines content. On the surfaces of the larger crystals multiple smaller lactose particles are present. The fines typically have an irregular shape. In accordance with the fines content determined by laser diffraction it seems that for Lactose RF the fines content is slightly lower than the one for Lactose EF and IF.

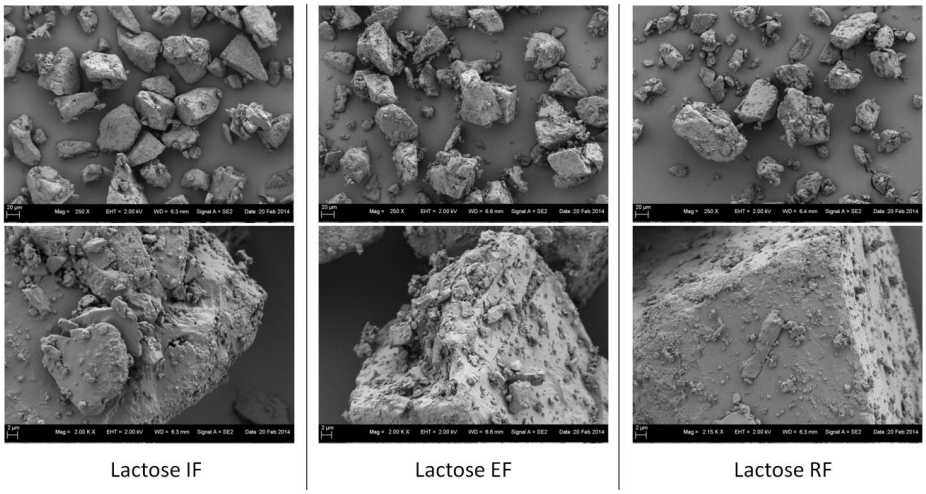

Figure 1 - SEM images of the three carrier materials

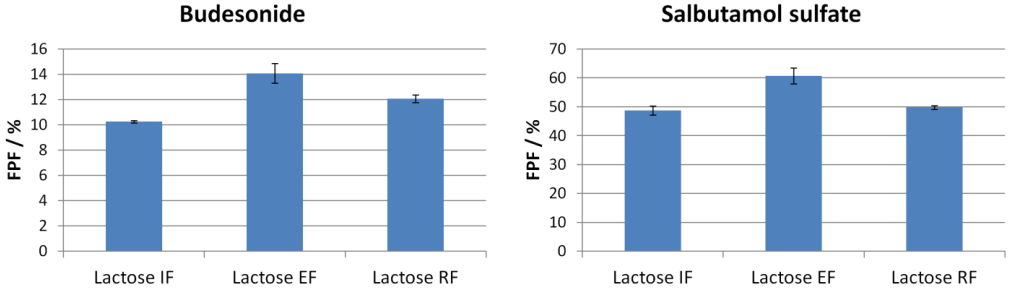

Figure 2 - Fine particle fractions of the adhesive powder blends containing 2% API (mean n=3±SD)

Figure 2 shows the fine particle fractions of the adhesive powder blends. Generally, the blends containing 2% budesonide have a lower fine particle fraction than those containing 2% salbutamol sulfate. This behavior has already been seen before and is attributed to the different adhesive and cohesive properties (hydrophilic vs. hydrophobic surface) and the different shape and particle size distribution of the APIs [6].

For both APIs the addition of extrinsic fines to the carrier material with reduced fines resulted in an increase of the fine particle fraction. Whereas the difference is only little for budesonide (12% vs. 14 %) it is much larger for salbutamol sulfate (50% vs. 61%). Interestingly there was no improvement of the FPF when using the lactose grade with intrinsic fines. The same (salbutamol sulfate, 49%) or even lower values (budesonide, 10%) as for lactose RF were obtained. The de-agglomeration of the powder blends seems to differ in dependence of weather the lactose fines are intrinsic or if they are added afterwards. When adding later via a mixing process the fines have the chance to preferably locate at spots with higher surface energy. Additionally the differences could arise due to the fact that the shape of the fines and the particle size distribution as well as other parameters such as amorphous content (although below 1%) probably differ as the intrinsic fines are produced via crystallization and the extrinsic fines via milling. Also the adhesion of the fines likely differs. The intrinsic fines may adhere to the surface more firmly as during drying solid bridges between the fines and the carrier surface can form.

No correlation between the physico-chemical properties such as amorphous content or surface energy of the carrier combinations and the FPF could be established. For lactose IF (45.51±0.83 mJ/m^2) and lactose EF (45.52±0.23 mJ/m^2) the surface energy was identical whereas the value was lower for lactose RF (38.44±0.09 mJ/m^2). However the FPF showed the largest differences when comparing the formulation with lactose IF and lactose EF.

Conclusion

This study shows that is important whether the fines content is intrinsic or if it is externally added. Intrinsic fines in this case do not increase the inhalable fraction as they might not be preferentially located at spots with higher surface energy. Additionally their physico-chemical properties such as shape, particle size distribution or amorphous content likely differs due to the different production process (crystallization vs. milling). For salbutamol sulfate the effect of the addition of fines was more pronounced than for budesonide. The physico-chemical properties of the carrier combinations assessed in this study such as amorphous content and surface energy did not correlate with the FPF.

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