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Effect of milling and sieving on functionality of dry powder inhalation products

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Abstract

α-Lactose monohydrate is the standard excipient used as diluent or carrier in dry powder inhaler (DPI) formulations. Earlier studies have already revealed that raw materials for the production of inhalation grade lactose have to be carefully selected in order to avoid batch-to-batch variability. In the present study, the effect of milling and milling intensity on the flow properties and the physico-chemical characteristics of lactose crystals has been determined. The milled lactoses were then further processed by sieving to give lactose qualities with identical size distribution data, but different batch history (non-milled and milled at different conditions). These were then used to manufacture low concentration (0.25%) drug blends with the model drugs salbutamol sulphate (SBS) and beclometasonedipropionate (BDP); the blends were analysed with a Multistage Liquid Impinger (MLI) after delivery from an Easyhaler® and an Aerolizer® device. It could be shown that gentle milling already results in surface defects on the lactose crystal which are further enhanced by using a higher milling intensity. Produced fine lactose particles during the milling process strongly adhere to the lactose surface and cannot be removed by compressed air which is used for the particle sizing. By trend, a higher milling intensity resulted in higher fine particle fractions (FPF) with both devices. Also, SBS was found to generally give higher fine particle fractions than BDP, independent from the device used. In conclusion, lactose pre-treatment by gentle or strong milling affects the carrier surface and thereby the aerosolization properties of drug/lactose blends produced.
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Keywords: Lactose for inhalation; Salbutamol sulphate; Beclometasonedipropionate; Carrier; Raw material; Milling

1. Introduction

Dry powder inhalers (DPIs) are the major alternative to pressurized metered-dose inhalers (pMDI) having the immediate obvious 'green' advantage because they are not dependent on propellants. Since the 1960s, the development of DPI drug products has tremendously increased because this dosage form offers some advantages over the commonly used MDI for respiratory delivery of drugs (Smith and Parry-Billings, 2003): DPIs are typically breath-actuated, they are in several cases re-loadable, newer devices do contain a dose counting mechanism and they can be used for both high and low dose entities as well as for peptide and protein drugs (Wall, 1995).

Although the development of a dry powder inhaler typically covers device development, process development and powder formulation development, the academic and industrial focus is fixed on powder development, as can be seen from the huge quantity of contributions in the scientific literature and the patent landscape (Niven, 2002). The development of a dry powder formulation can be further sub-divided into the development of the micronized drug particle production process, e.g. the milling process (Ticehurst et al., 2000), supercritical fluid processing (e.g. Kerc et al., 1999), spray-freezing into liquid (Rogers et al., 2002), in situ micronization (Rasenack et al., 2003) to list a few of the techniques; and the development of a suitable carrier system (e.g. French et al., 1996; Staniforth, 1995; Ganderton and Kassem, 1991; Steckel and Bolzen, 2004). So far, lactose monohydrate still is the carrier of choice because it is an inert, cheap, broadly available and non-toxic excipient (teWierik and Diepenmaat, 2002). However, it has been recognized in several earlier studies that the efficiency of a powder formulation is highly dependent on the lactose quality and source (Steckel, 2002), the size distribution of the used lactose carrier (Zeng et al., 1996) and the content of fine lactose (Lucas et al., 1998a,b) or

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ternary additive particles (Kassem, 1990; Begat et al., 2001) and with respect to the used dry powder inhaler the flow properties of the device (Kaye, 1997). Differences in surface topology, surface energy and air-entrainment behaviour of the used lactose crystals were suggested to be responsible for these dependencies (Price et al., 2002). In a recent study, the influence of size distribution parameters of the raw material lactose which is an intermediate product of the final inhalation grade lactose on the efficiency of a DPI formulation has been analysed. Although this study, which revealed differences in inhalation product efficiency, offered the unique advantage that all materials were taken from the same supplier and were processed by full scale equipment, a direct link of one or more physico-chemical parameters to efficiency could not be established. Therefore, the functionality of lactose should be further elucidated by manufacture of lactose crystals which do not (or only slightly) differ in the size distribution parameters but which were processed underlying different energy inputs during the production. For this purpose, one raw material batch of lactose was selected and was divided into three sieve fractions (50–77 μm, 77–120 μm and 166–210 μm) by vibrational sieving. The same raw material lactose was then milled in a classifier mill at 3000 and 6000 rpm and afterwards separated into the same three sieve fractions. Again, emphasis is put on the fact that all production steps have been done by using industrial production scale equipment and not, as in most other studies analysing the influence of lactose as drug carrier in dry powder inhalations, with laboratory equipment. Beclometasonedipropionate (BDP) and salbutamol sulphate (SBS) were used in a low drug-to-carrier ratio as model drug substances for the preparation of powder blends; the powder blends were then delivered to a Multistage Liquid Impinger (MLI) by means of an Aerolizer® and an Easyhaler® device for functionality testing. Simultaneously, physico-chemical aspects such as size distribution, specific surface area, rugosity, surface energy, vapour sorption behaviour and amorphous content, were analysed for the used sieve fractions.

2. Materials and methods

2.1. Materials

One commercial batch of lactose monohydrate (Lactochem® LC204 crystals) was donated by Borculo Domo Ingredients (Zwolle, The Netherlands). Salbutamol sulphate with a volume mean diameter of 4.1 μm, batch no. SSI1101131, was purchased from Welding AG (Frankfurt, Germany) and beclometasonedipropionate with a volume mean diameter of 3.3 μm, batch no. FP02142B, came from Fährhaus Pharma GmbH (Hamburg, Germany). All other reagents used were of analytical quality, reagents for HPLC analysis of chromatography quality, and were supplied by Merck KGaA (Darmstadt, Germany). The water used was of double distilled quality.

2.2. Methods

2.2.1. Preparation of lactose sieve fractions

From the Lactochem® crystals a range of milled materials was produced on an industrial classifier mill with varying mill speeds of 1000, 2000, 3000, 4000, 5000 and 6000 rpm. The classifier function of the mill was not used which implies that all powder particles pass the mill once during each milling run. Based on the size distribution data of the resulting milled products (Table 1) the raw material and the milled products obtained at 3000 and 6000 rpm, respectively, were selected for further processing with a SWECO sieve separator (Sweco, Nivelles, Belgium) using two sieve screens per sieving process. For all sieving processes the middle fractions were further used; fine particles were removed from the middle fractions by sieving on a one screen sieve, using the under sieve of the corresponding first sieving process. The sieving on the one screen sieve was repeated until no change in particle size distribution was observed any more. The following seven sieve fractions were used:

- from the raw material (Lactochem®): 50–77 μm, 77–120 μm and 166–210 μm;
- from the product milled at 3000 rpm: 50–77 μm and 166–210 μm;
- from the product milled at 6000 rpm: 50–77 μm and 166–210 μm.

2.2.2. Blending/homogeneity analysis

All drug/lactose powder blends were manufactured according to a fixed protocol. Briefly, the drug and the lactose were sieved (355 μm sieve) and weighed into a cylindrical stainless steel mixing vessel using the sandwich method. The powder was

Table 1
Size distribution parameters of the lactose raw material, the received milling fractions and the used model drugs

Mill speed (rpm)	d10 (μm)	d50 (μm)	d90 (μm)	<15 μm (%)	<45 μm (%)	<105 μm (%)	<150 μm (%)	<215 μm (%)
Raw	59.2	148.5	235.2	2.8	7.4	24.8	50.9	85.1
1000	31.2	125.6	209.3	5.8	13.6	37.6	64.8	91.8
2000	35.4	130.3	210.3	5.2	12.3	34.6	62.3	91.7
3000	38.3	133.3	213.6	4.8	11.5	33.1	60.3	90.5
4000	37.0	133.0	214.6	5.0	11.9	33.5	60.3	90.1
5000	18.0	107.7	196.8	8.7	20.8	48.4	73.4	94.4
6000	12.1	85.6	176.6	12.0	28.8	60.5	81.7	97.1
SBS	1.7	4.1	9.1	n.d.	n.d.	n.d.	n.d.	n.d.
BDP	0.94	3.3	7.99	n.d.	n.d.	n.d.	n.d.	n.d.

n.d. not determined.

mixed for 30 min at 24 rpm in a Turbula blender (W. Bachofen AG, Switzerland), sieved (355 μm sieve) and mixed for another 30 min. The final mix was sieved again and stored tightly closed in an aluminium container. Blends with a drug-to-carrier ratio of 1:400 (0.25%, w/w) were produced and analysed. The homogeneity of the powder blend was determined by randomly taking ten samples from the top, the mid and the bottom of the powder blend. The drug content was assayed by a validated HPLC method. Average content, standard deviation (S.D.) and relative standard deviation (R.S.D.) were calculated; the requirements were met and the powder was used for further testing if the R.S.D. was <3%.

2.2.3. Particle size distribution

The particle size distribution of the raw materials (Lactochem®), the inhalation grade lactose and the drug was done using a Sympatec HELOS laser diffractometer (Sympatec, Clausthal-Zellerfeld, Germany). The powders were dispersed by compressed air (2 bar) into the measuring zone of the laser and focussed onto the detector with a 20 mm lens (micronized drug) and a 100 mm lens (lactose qualities), respectively. All tabulated data given represent the average values of at least ten determinations.

2.2.4. Specific surface area

The specific surface area of the powders was measured with the BET gas adsorption method. Powders were prepared under vacuum for 1 h at 40 °C and then analysed using a Gemini 2360 BET surface area analyzer (Micromeritics, Norcross, USA). Calculation of the specific surface area was done by the BET multipoint method. All measurements have been done in triplicate.

2.2.5. Rugosity

As a shape parameter of the lactose crystals the surface rugosity has been calculated according to Eq. (1):

$$R = \frac{\mathrm{SSA_{BET}}}{\mathrm{SSA_{LD}}} \quad (1)$$

where $\mathrm{SSA_{BET}}$ is the measured specific BET surface area and $\mathrm{SSA_{LD}}$, the calculated surface area of the particle volume distribution assuming spherical shape of the particles.

2.2.6. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) scans of all lactose monohydrate batches were taken by a Perkin-Elmer DSC 7 (Perkin-Elmer, Connecticut, USA) at a heat rate of 10 °C/min.

2.2.7. Dynamic vapour sorption (DVS)

The amorphous content of the lactose batches as well as the sorption/desorption profiles of the lactoses were determined with a DVS 1 (Surface Measurement Ssystems, London, UK) using a validated method (Markefka and Steckel, 2002) enabling the quantitation of amorphous lactose on the crystal surface as low as 0.5% (w/w).

2.2.8. Scanning electron microscopy (SEM)

SEM pictures were taken with a Philips XL 20 SEM (Philips, Eindhoven, The Netherlands). Samples were fixed on a double-sided adhesive tape and sputter-coated with gold in an argon atmosphere at 50 mbar with a sputter coater Baltec SCD 005 (Bal-Tec AG, Balzers, Liechtenstein).

2.2.9. Flow properties

Both the raw material and milled products were characterised on a Hosokawa Micron Powder Characteristics Tester (Hosokawa Micron Corporation, Osaka, Japan). Compared with the common methods of powder characterisation, this instrument offers the opportunity of several automated test set-ups within one apparatus and information on Carr's index, angle of repose and the angle of spatula are obtained.

2.2.10. Impinger analysis

The powder blends were aerodynamically assessed with a Multistage Liquid Impinger as described in European Pharmacopoeia (2001). Two different devices were used for the delivery of the powder blends. The Easyhaler® was chosen as an example for a reservoir based, medium resistance device and the Aerolizer® as an example for a low resistance, capsule-based inhaler. One gram of the powder blend was filled into the Easyhaler®, the inhaler shaken as described in the user instructions and tightly connected to the metal inlet of the impinger. Forty consecutive doses were released into the impinger. The airflow through the impinger was adjusted to 4 kPa pressure drop across the inhaler resulting in a flow rate of 51 l/min in case of the Easyhaler® and of 100 l/min in case of the Aerolizer®. For testing with the Aerolizer®, size 3 gelatin capsules were filled with approximately 20 mg of the powder blend and 20 capsules delivered into the impinger. Samples of all stages, the filter and throat fraction were collected and analysed by means of a validated HPLC method.

3. Results and discussion

3.1. Physico-chemical characteristics of the produced lactose batches

The raw material lactose batch was milled at different mill speeds (1000–6000 rpm) in order to comminute the lactose and to induce irregularities and surface defects on the lactose crystals. Table 1 summarizes the size distribution data of the obtained milled powders. It can be seen that gentle milling (1000–4000 rpm) reduces the mean particle size and increases the fine fraction in the powders. However, only a minor influence on the particle size distribution at mill speeds in this range was observed. Milling at higher mill speeds (5000–6000 rpm) further reduces the average particle size (from a d50% of 149 μm of the raw material to 86 μm after milling at 6000 rpm) and increases the fines content. Eighty percent of the milled lactose (6000 rpm) is now below 150 μm compared to only 50% of the raw material.

The milled batches were now further classified into three sieve fractions: 50–77 μm, 77–120 μm and 166–210 μm. Only the raw material and milled lactose at 3000 and 6000 rpm were

Table 2
Size distribution characteristics of the seven sieve fractions used further for blending and impinger testing

Lactose sieve fractions	d10 (μm)	d50 (μm)	d90 (μm)	<15 μm (%)	<45 μm (%)	<105 μm (%)	<150 μm (%)	<215 μm (%)
50–77 μm (raw material)	49.8	79.7	123.4	2.2	6.7	79.7	96.8	99.8
50–77 μm (3000 rpm)	43.8	72.3	110.7	3.8	10.6	87.8	99.0	100.0
50–77 μm (6000 rpm)	42.4	72.1	109.2	4.6	11.3	88.4	98.8	99.9
77–120 μm (raw material)	80.3	126.4	186.4	1.6	2.6	28.6	71.0	97.1
166–210 μm (raw material)	125.0	190.5	250.4	2.0	2.9	6.3	20.1	70.3
166–210 μm (3000 rpm)	127.3	192.3	251.4	2.9	3.6	5.9	18.9	68.6
166–210 μm (6000 rpm)	127.8	192.7	251.5	3.5	4.2	6.1	18.5	68.4

processed because the other milled products did not show significant differences with respect to the size distribution. As can be seen from Table 2, the particle size distributions of the produced sieve fractions are fairly similar for the raw lactose and for the selected milled products and show only minor deviations in terms of the size distributions data (e.g. d50% of 190.5, 192.3 and 192.7 μm for the size fraction 166–210 μm, raw material, milled at 3000 and 6000 rpm, respectively). Interestingly, the specific surface area was found to deviate slightly for the sieve fractions (Table 3), depending of the milling status: the non-milled quality principally showed the lowest specific surface area whereas higher milling intensities led to higher specific surface areas, although the differences in the size distribution data only were insignificant ($p = 0.05$). This indicates that the milled material contains a larger portion of fine particles which were not detected during the size distribution analysis. It is worth noting that no amorphous content was found in any of the materials, neither in the raw material nor in the gently and strongly milled batches. Most likely, re-crystallization has already taken place during storage and transportation of the bulk materials (Darcy and Buckton, 1998).

The produced lactose grades also differ from the visual aspect as can be seen from the SEM photographs (Fig. 1). A higher milling intensity resulted in higher adhering fines content. Obviously, the adhesion of the produced fine material is that strong that it cannot be removed by the compressed air that is used for the dispersion of the powders for the particle size analysis. Also, the surface of the milled material appeared to be smoothened by the milling procedure.

With respect to the calculated rugosity (ratio of BET surface and assumed surface of spherical particles by laser diffraction), the rugosity appears to decrease with higher milling intensities, although the BET surface area is slightly higher in the milled products. This observation may be attributed to the effect that particles are smoothed and rounded during the milling procedure; however, this discrepancy already indicates the limitations of these two parameters to differentiate between the materials.

3.2. Flow properties of raw material and processed lactoses

The data obtained by the Hokosawa Micron Powder Characteristics Tester are summarized in Table 4. Considering the data of the Carr's index, one can see the same trend in the different fractions. As expected, the 166–210 μm fraction shows the best flowability which is independent on the milling intensity. Regarding the flow properties of the three 166–210 μm fractions the angle of spatula of the material coming from the most strongly milled product is deviating pointing to poorer flowability than the 166–210 μm fraction from the two other materials. Possibly the stronger milling resulted in more cohesion, leading to less flowability. Moreover, the higher angle of spatula may result in dosing problems from reservoir type inhalers. In the case of the three fine fractions 50–77 μm, the material from the un-milled feed shows better flow than the milled materials. The data marked as angle of repose and angle of spatula are difficult to interpret. As known by former studies, these data are depending on many parameters and cannot be transferred to a binary inhalation mixture made by these materials.

3.3. Aerodynamic assessment of drug/lactose blends

The aerosolization properties of the different lactose grades were tested with drug powder blends using the model drugs

Table 3
Physico-chemical characteristics of the seven sieve fractions used further for blending and impinger testing

Lactose sieve fractions	BET surface (m^2/g)	Amorphous content (%)	Density (g/cm^3)	Rugosity
50–77 μm (raw material)	0.20	<0.5	1.5420	1.44
50–77 μm (3000 rpm)	0.25	<0.5	1.5400	1.40
50–77 μm (6000 rpm)	0.25	<0.5	1.5379	1.30
77–120 μm (raw material)	0.14	<0.5	1.5381	1.50
166–210 μm (raw material)	0.12	<0.5	1.5377	1.64
166–210 μm (3000 rpm)	0.14	<0.5	1.5369	1.70
166–210 μm (6000 rpm)	0.15	<0.5	1.5387	1.56

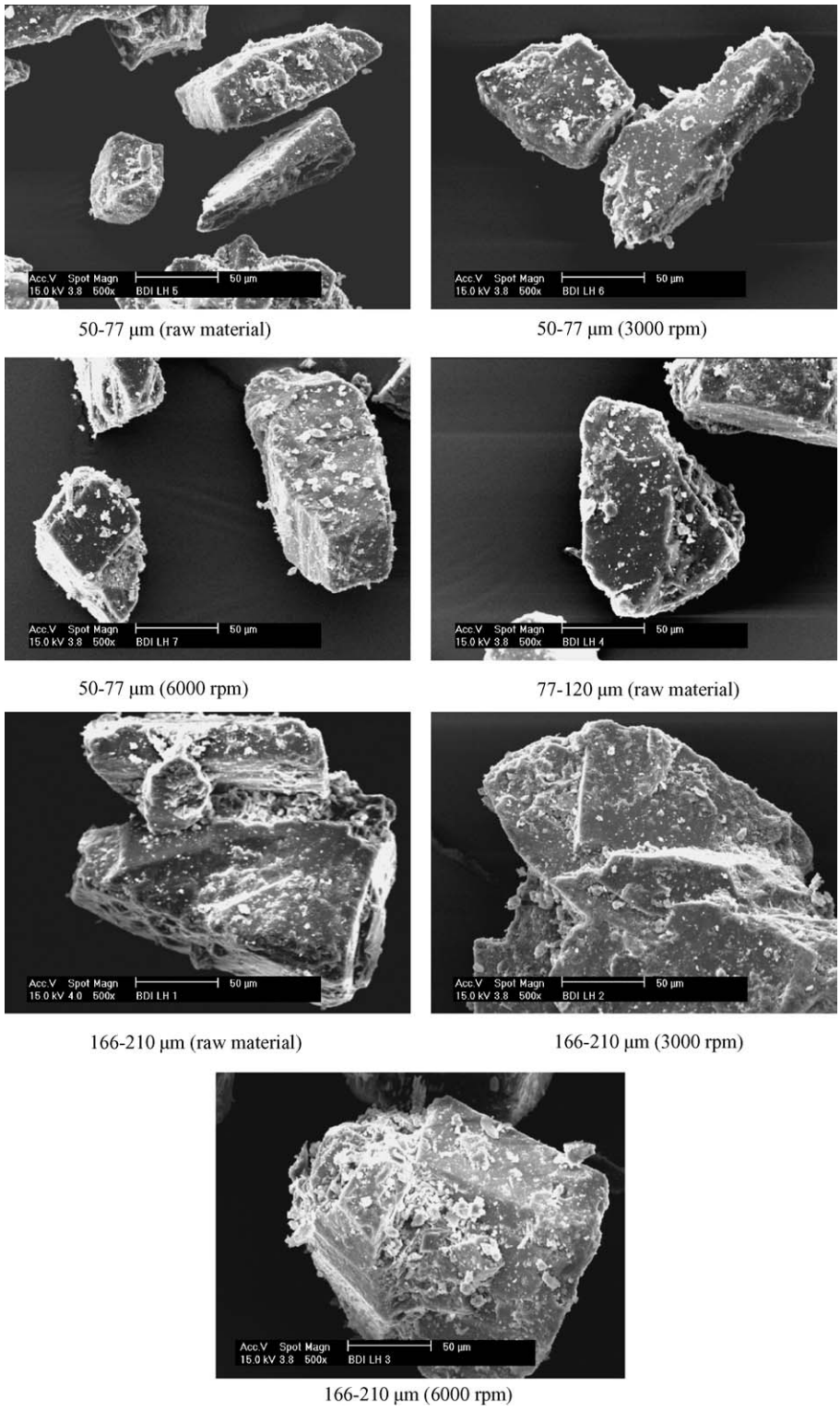


Fig. 1. SEM photographs of the seven batches of lactose produced by milling and sieving.

beclometasonedipropionate and salbutamol sulphate in a very low concentration as this low drug concentration was shown to have the power to discriminate between lactose batches. Powder blends were delivered both with the Easyhaler® and the Aerolizer® device.

3.4. Salbutamol sulphate/lactose blends

The deposition data obtained with the different SBS/lactose blends delivered from two different devices underlined that efficiency is dependent on both, the device and the formulation.

Table 4
Flow properties of the raw material and the seven sieve fractions used further for blending and impinger testing

Lactose sieve fractions	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Angle of repose (°)	Angle of spatula (°)
Raw	0.70	0.85	22	34	52
50–77 μm (raw material)	0.69	0.81	16	40	52
50–77 μm (3000 rpm)	0.67	0.82	23	39	58
50–77 μm (6000 rpm)	0.66	0.79	20	38	57
77–120 μm (raw material)	0.72	0.82	13	35	45
166–210 μm (raw material)	0.67	0.76	13	36	35
166–210 μm (3000 rpm)	0.70	0.77	11	36	34
166–210 μm (6000 rpm)	0.71	0.78	9	34	41

Generally, the sieve fractions produced from the non-milled raw material resulted in lower fine particle fractions (FPF) as compared to the milled materials (Fig. 2a, Table 5).

Delivery from both devices is efficient but showed slight differences between the Aerolizer® and the Easyhaler®. The unprocessed material disperses better from the Aerolizer®: 33.6% FPF versus 20.2% FPF for the sieve fraction 50–77 μm and 26.6% FPF versus 22.8% FPF for the sieve fractions 166–210 μm. The sieve fraction 77–120 μm did not reveal any differences with SBS in the impinger test. A higher milling intensity resulted by trend in a higher fine particle fraction with both devices. Again, differences between devices and sieve fractions can be

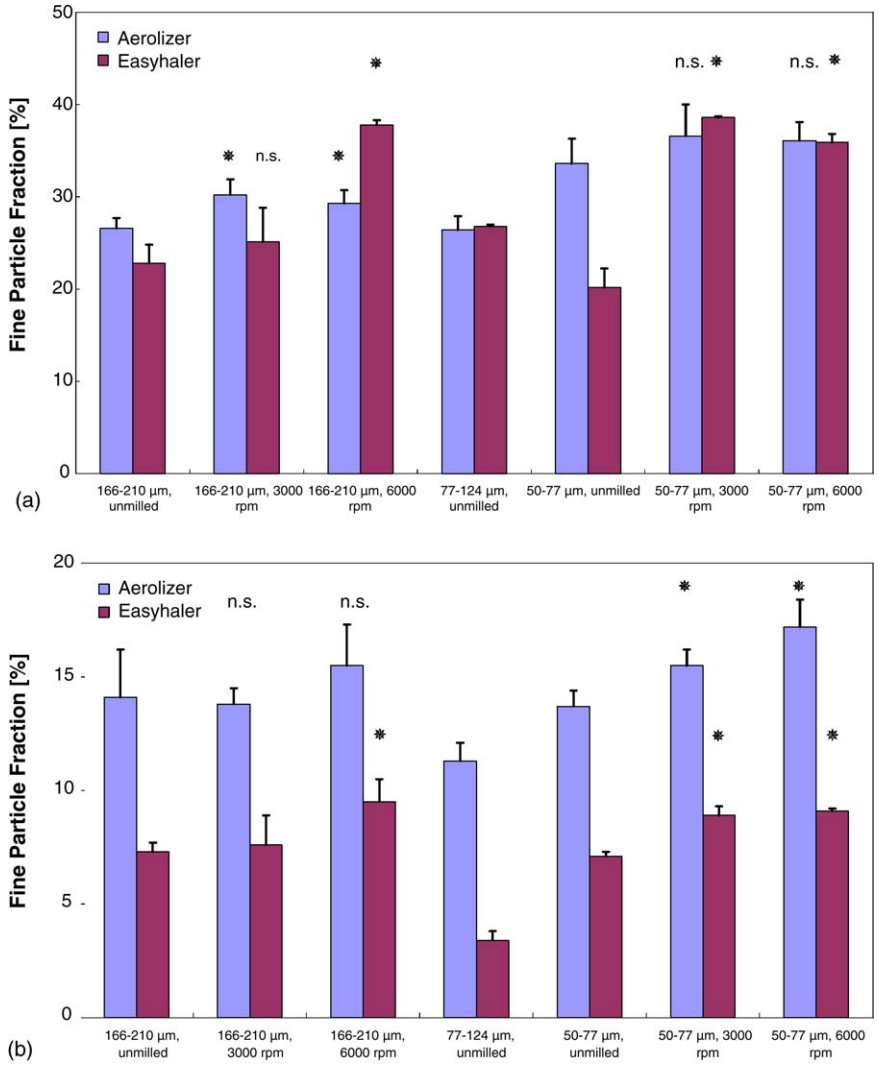


Fig. 2. (a) Influence of lactose pre-treatment on fine particle fraction of salbutamol sulphate powder blends (error bars = S.D.); (*) significant, n.s. non-significant difference to the non-milled material of the same sieve fraction, $p = 0.05$. (b) Influence of lactose pre-treatment on fine particle fraction of beclometasone dipropionate powder blends (error bars = S.D.); (*) significant, n.s. non-significant difference to the non-milled material of the same sieve fraction, $p = 0.05$.

Table 5
Per stage deposition data of the drug/lactose blends as determined with a Multistage Liquid Impinger, calculated as percentage of emitted dose (S.D. was in all cases lower than 3%)

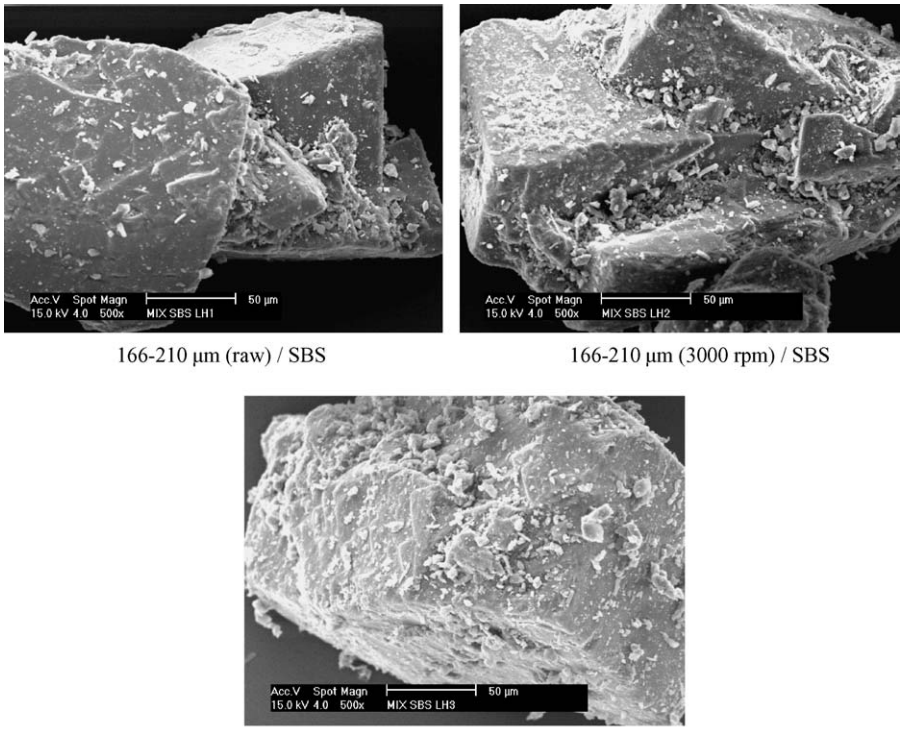
	166–210 μm unmilled	166–210 μm 3000 rpm	166–210 μm, 6000 rpm	77–124 μm, unmilled	50–77 μm, unmilled	50–77 μm, 3000 rpm	50–77 μm, 6000 rpm
Salbutamol sulphate/Aerolizer®							
Retention (%)	14.1	16.8	15.1	12.8	6.2	7.8	8.6
Throat (%)	9.4	11.2	12.3	10.0	10.3	11.0	10.9
S1(PS) (%)	45.1	36.9	38.8	44.7	41.6	36.0	32.9
S2 (%)	7.8	9.2	8.1	8.7	9.3	10.2	13.2
S3 (%)	10.3	11.9	11.7	11.8	16.4	18.2	20.6
S4 (%)	8.0	10.2	9.9	9.1	11.4	12.9	12.0
F (%)	5.2	3.8	4.1	2.9	4.8	3.8	1.7
Salbutamol sulphate/Easyhaler®							
Retention (%)	–	–	–	–	–	–	–
Throat (%)	13.0	13.3	15.6	11.5	16.9	15.2	14.1
S1(PS) (%)	57.3	53.7	35.7	52.2	50.6	32.5	35.5
S2 (%)	2.8	3.0	3.8	4.0	5.6	5.4	6.0
S3 (%)	8.3	9.7	14.2	11.0	13.4	16.6	17.0
S4 (%)	12.6	14.5	20.7	15.8	10.4	21.1	20.0
F (%)	6.1	5.8	9.9	5.5	3.1	9.2	7.3
Beclometasone dipropionate/Aerolizer®							
Retention (%)	11.7	11.1	10.9	8.7	8.2	14.4	11.8
Throat (%)	12.2	11.1	12.6	10.1	8.4	8.7	9.6
S1(PS) (%)	55.7	57.3	54.3	64.8	63.4	55.3	54.2
S2 (%)	7.3	7.7	7.8	5.6	6.6	7.6	8.4
S3 (%)	8.0	8.5	9.3	7.4	8.8	9.3	10.8
S4 (%)	4.0	3.6	4.0	2.8	3.6	3.9	3.7
F (%)	1.0	0.8	1.1	0.6	0.9	0.8	1.4
Beclometasone dipropionate/Easyhaler®							
Retention (%)	–	–	–	–	–	–	–
Throat (%)	16.4	22.0	23.6	16.6	18.4	21.4	19.9
S1(PS) (%)	71.0	64.9	59.4	75.9	68.0	61.1	62.8
S2 (%)	2.8	2.9	3.9	2.8	3.5	4.7	4.4
S3 (%)	5.1	5.9	7.0	3.2	5.7	7.3	7.5
S4 (%)	3.3	3.4	4.4	1.2	3.1	3.8	4.0
F (%)	1.4	1.5	1.3	0.4	1.3	1.3	1.3

seen: The finer lactose material (50–77 μm) already gave a significant improvement of the fine particle fraction after milling at 3000 rpm whereas a significant increase of the FPF becomes obvious at high mill speed for the sieve fraction 166–210 μm (Fig. 2a). With the coarser material, a better dispersibility was found with the Easyhaler® whereas the Aerolizer® was able to disperse the fine-powdered blend in a better way. It has also to be noted that the produced sieve fractions of the raw material only resulted in slight differences with respect to the fine particle fraction, again with the trend that the fine lactose gave a higher fine particle fraction with the Aerolizer® device (Fig. 2a).

3.5. Beclometasonedipropionate/lactose blends

The dispersibility of the BDP/lactose blends was generally on a lower level compared to the SBS data with the Aerolizer® giving higher fine particle fractions than the Easyhaler® device. The same trend as described for the SBS/lactose blends can be observed, i.e. that higher mill speed tend to produce higher fine particle fractions. Especially, the fine fractions (50–77 μm) of the milled materials produced significantly higher fine particle fractions than the unprocessed materials (Fig. 2b).

A major reason for the different aerosolization behaviour of the unprocessed and processed lactose qualities can be seen in the modified surface structure of the lactose crystals: the un-milled quality only contains few fine particles and exhibits a partly rough-structured surface whereas the milled material shows a considerable amount of fine lactose particles that have been produced during milling but adhere strongly to the surface so that they cannot be removed by compressed air (Fig. 3). Similarly, they will also not be removed during mixing with the micronized active material. As the corraded fine lactose is preferentially placed in edges and clefts of the lactose crystals, the drug becomes adhered to the smoother surface of the crystal where it can be removed more easily. Accordingly, the pretreated lactose resulted in higher fine particle fractions as the un-treated lactose. From the SEM photographs, it also becomes obvious that the produced fine lactose particles that are fixed to the coarser particles do not form agglomerates or “multiplets” as described by Lucas et al. (1998). The formation of multiplets and enhancement of dispersibility by this mechanismn was observed for higher contents of fine lactose and micronized drug. In this study, the drug concentration was held on an extremely low level to investigate influences in low-dose-dry-powder formulations.



166-210 µm (raw) / SBS

166-210 µm (3000 rpm) / SBS

166-210 µm (6000 rpm) / SBS

Fig. 3. SEM photographs of the salbutamol sulphate/lactose blends (only examples of the produced blends).

Table 5 lists the detailed deposition data for the investigated drug/lactose blends. All powder blends showed good emptying of the device and only little device retention in the range of 6–15% of the emitted dose for the Aerolizer® device. Device retention in the Aerolizer® was higher for the coarse sieve fractions of lactose and increased with higher milling intensity. Empyting of the gelatine capsules is dependent on the size of the used carrier lactose (Steckel et al., 2004a,b) and too large crystals, as represented by the fraction 166–210 µm, may be retained within the capsule together with the adhering fines. Device retention was generally lower for the sieve fraction 50–77 µm and also increased with higher milling intensity indicating more adhesion to the capsule wall. However, carrier particles are removed more completely from the capsule and release from the small crystals is enhanced due to occupation of the high energy sites by the adhering fine lactose crystals (Table 5).

4. Conclusions

The current study has shown the effect of milling and milling intensity on the aerodynamic behaviour of drug/lactose blends manufactured with the different grades of lactose. The effect of milling still can be observed although the sieve fractions of the produced batches did not differ significantly in terms of the particle size distribution. Milled and fractionated lactoses resulted in higher fine particle fractions than the non-milled material with the same size distribution. This effect is attributed to the produced fine material that adheres to the surfaces of the larger crystals, hindering the drug to settle in the surface clefts of the lactose crystal and, consequently, leading to improved aerosolization behaviour. The delivery performance, i.e. device emptying and device retention, was not observed to be different for the produced lactose qualities.

The study also underlined that different drugs behaved differently in the same inhaler device and different inhalers perform differently when used with the same drug blend.

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