Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 57 (2004) 495–505
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Functionality testing of inhalation grade lactose

H. Steckel[a,*], P. Markefka[a], H. teWierik[b], R. Kammelar[b]

[a]Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University of Kiel, Kiel, Germany
[b]Borculo Domo Ingredients, Zwolle, The Netherlands

Received 1 October 2003; accepted in revised form 9 December 2003

Abstract

Lactose monohydrate for inhalation is commonly produced by sieving out customer-specific size fractions of a crystallized bulk material of lactose. It was the aim of this study to investigate the influence of the raw material on the physico-chemical properties of the inhalation grade lactose and on the efficacy of powders for inhalation produced from these batches. The selected raw material lactose batches differed in the size distribution characteristics, the fines and the agglomerate content. These differences in the raw material could also be found to a smaller extent in the intermediate products and could not be completely levelled out in the final inhalation grade lactose.

Efficiency testing was done using salbutamol sulphate in two different concentrations (drug-to-carrier ratio of 1:36 and 1:400) as a model drug; the powder blends were delivered using the Aerolizer® and the Easyhaler® device. With the high drug load, nearly no differences could be observed between both the delivery systems and the different produced lactose batches. The fine particle fraction (FPF) (% $<$ 5 μm) was on a high level of $>$39% in all cases. With the low drug load significant differences between the devices and the lactose batches were found. The FPF was distinctly reduced to 15–30%, with the Easyhaler® generating a higher fraction of fine particles than the Aerolizer® device. Although the observed differences between the lactose batches could not be linked to one specific physico-chemical parameter determined for the carrier, they led to the conclusion that the differences between the test batches of inhalation grade lactose especially manufactured for this study can affect the functionality of an inhalation powder. The effects are significantly smaller with high drug load formulations than using a low drug concentration.

Keywords: Lactose for inhalation; Salbutamol sulphate; Carrier; Raw material; Surface properties

1. Introduction

Pulmonary delivery of both locally and systemically acting drugs is still in the focus of interest [1]. While metered dose inhalers (MDIs) are still widely used devices, especially for rescue medication, the absolute number of MDI products is decreasing due to the phase out of chlorofluorocarbons and the limited availability of alternative products with hydrofluorocarbon propellants [2]. On the other hand, dry powder inhalers (DPIs) are an upcoming alternative with a variety of different devices so far described in the literature [3]. Pulmonary application of micronized actives via DPIs is also a promising alternative for protein and peptide drugs which, until now, need to be administered parenterally [4].

Most of the marketed dry powder inhalation products use a carrier-based powder formulation consisting of the micronized active and an overage of a coarse carrier material, most commonly lactose monohydrate. A typical ratio of drug-to-carrier is a ratio of 1:67.5 as described in the literature [5]. Although lactose monohydrate is a well known and well characterized excipient, the quality of lactose—sieved or milled quality, source of lactose—used for the formulation of an inhalation powder is of utmost importance and significantly influences the efficiency of the product [6]. It has also been reported that the particle size and the size distribution of lactose in a DPI formulation affects the aerosolization properties of the powder [7]. Surface roughness and shape of the carrier particles were also described to have a major influence on the adhesion of drug particles to the surface of the carriers and methods to reduce the strong drug-to-carrier adhesion have been

* Corresponding author. Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University of Kiel, Gutenbergstrasse 76, D-24118 Kiel, Germany. Tel.: +49-431-880-1336; fax: +49-431-880-1352.
E-mail address: steckel@pharmazie.uni-kiel.de (H. Steckel).

0939-6411/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2003.12.003

proposed: Staniforth et al. [8] propose a corrasion process as pre-treatment of the carrier material in a ball mill or a high shear mixer. During this process, surface clefts and irregularities of the lactose crystals are covered by the fine lactose particles that are generated during the process. According to the hot spot theory a pre-blending of the coarse carrier with micronized lactose also leads to improved dispersibility of the powder blend because the fine lactose is mainly attached to the high energy sites on the lactose crystal whereas the drug particles, being added in a second mixing step, are much weaker bond to the surface [9]. Another approach, as described by Ganderton and Kassem [10], is to smooth the surface of the lactose crystals either by pre-treatment of the lactose crystals in an organic solvent [10] or to influence the surface texture by addition of polyacrylic acid to the crystallization medium [11]. Although, all these approaches tended to improve the separation of drug from the carrier during inhalation, their practical use in marketed products is fairly limited. Despite all these formulation tricks, the reliability of a DPI product is mainly influenced by the batch-to-batch consistency of the lactose quality used, i.e. the control of manufacturing process for a specified lactose quality. The industrial manufacture of lactose monohydrate crystals is a semi-continuous, ton-scale process. For the production of inhalation grade lactose relatively small quantities of lactose are selected and processed further batch-wise by classifying or milling.

It was the aim of the current study to evaluate the influence of different raw material lactose batches on the physico-chemical properties of the resulting inhalation grade lactose batches and the aerosolization characteristics of powder blends with a model drug substance by using two different inhaler devices.

2. Materials

Four commercial batches of lactose monohydrate (Lactochem® crystals) and one development batch of lactose monohydrate were donated by Borculo Domo Ingredients (Zwolle, The Netherlands). Four lactose batches were specifically selected to give differences much higher than normally encountered batch-to-batch variations in routine production of inhalation grade lactose. Selection criteria were agglomerate content (arbitrarily defined as $\% > 150\ \mu m$), fines content ($\% < 45\ \mu m$ after air-jet sieving) and volume mean diameter (VMD). The development batch was manufactured to give an atypical particle shape (Table 1). From these five lactose batches, test batches of inhalation grade lactose were produced on a pilot scale according to the following fixed protocol (Fig. 1): sieving through a 146 and 91 μm sieve (SWECO sieve separator, Nivelles, Belgium) followed by air jet sieving (Alpine air jet sieve, Doetinchem, The Netherlands) of the middle fraction using a 45 μm sieve. All processing and the consecutive storage were carried out at ambient conditions, 21 °C and 45% RH. The physico-chemical characteristics of the resulting intermediate lactose fractions and the inhalation grade lactose are summarized in Tables 2 and 3.

Salbutamol sulphate (SBS) with an NMD of 4.1 μm, batch no. SSI1101131, was purchased from Welding AG (Frankfurt, 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.

3. Methods

3.1. Blending/homogeneity analysis

All SBS/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 mixed for 30 min at 24 rev./min 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 in two different drug-to-carrier ratios, 1:36 (as in the corresponding marketed Easyhaler® product) and 1:400 were produced and analysed. The homogeneity of the powder blend was determined by randomly taking 10 samples from the top, the mid and the bottom of the powder blend. The drug content was assayed by a validated HPLC

Table 1
Batch characteristics of raw materials (Lactochem® crystals)

Batch no.	Agglomerates	$\% > 150\ \mu m$	Amount fines	$\% < 45\ \mu m$	VMD	
115022 (aged batch)	Low	2.9	High	13.6	Low	96.9
205037	High	26.7	Low	4.7	High	168.4
204032	High	46.7	High	13.1	High	157.7
201001	High	17.7	Low	5.0	Low	124.9
150009	Low	5.8	High	11.0	Low	116.6

VMD, volume mean diameter.

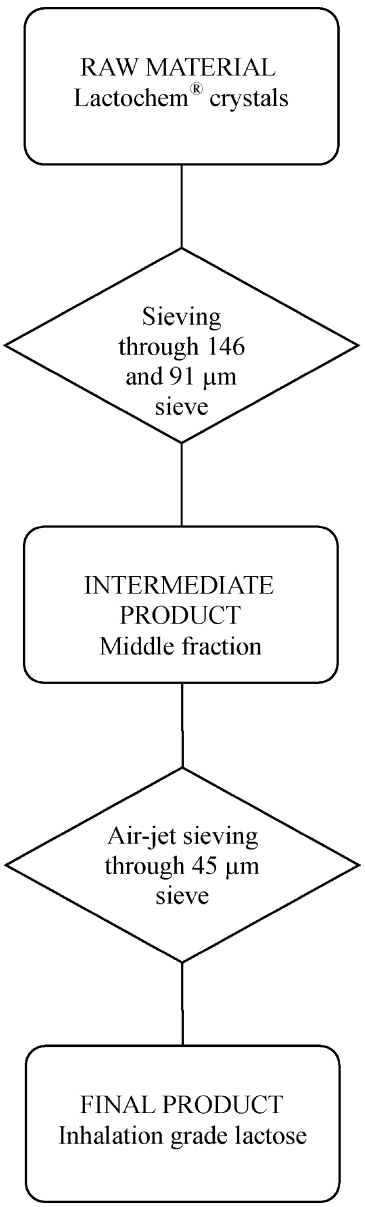

Fig. 1. Manufacturing steps carried out to obtain the 'inhalation grade lactose'.

method. Average content, standard deviation (SD) and relative standard deviation (RSD) were calculated; the requirements were met and the powder was used for further testing if the RSD was $<3\%$.

3.2. 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 data given represent the average values of at least 10 determinations.

3.3. 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 analyser (Micromeritics, Norcross, USA). Calculation of the specific surface area was done by the BET multipoint method. All measurements have been done in triplicate.

3.4. 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 $\mathrm{SSA_{LD}}$ is the calculated surface area of the particle volume distribution assuming spherical shape of the particles.

3.5. DSC

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

3.6. XRPD

X-ray powder diffraction patterns of the lactose batches were taken by means of an X-ray diffractometer with a rotating anode (Stoe and Cie GmbH, Darmstadt, Germany) with Cu Kα radiation (monochromator: graphite) generated

Table 2
Batch characteristics after sieving through 146/91 μm sieve (intermediate products)

Batch no.	Agglomerates raw material	Fines raw material	VMD raw material	d10% (μm)	d50% (μm)	d90% (μm)	<45 μm (%)
207067 (aged batch)	Low	High	Low	23.8	88.5	152.2	18.5
207068	High	Low	High	80.6	135.3	203.3	4.4
207069	High	High	High	57.9	108.3	149.6	7.7
207070	High	Low	Low	76.8	118.1	167.4	3.7
207071	Low	High	Low	37.6	106.0	166.3	11.6

Table 3
Physico-chemical properties of the raw material batches of lactose (Lactochem®) and the resulting inhalation grade lactose

	Particle size (μm)				BET surface (m^2/g)	Amorphous content (%)	Dispersive surface energy (mJ/m^2, RSD) (%)	Density (g/cm^3)	Rugosity
	d10%	d50%	d90%	% < 45 μm					
Lactochem® crystals									
LC 115022	27.9	96.9	196.7	18.91	0.1395	n.d.	–	1.5384	1.5605
LC 205037	72.6	168.4	262.9	7.04	0.0806	<0.5	–	1.5390	1.5857
LC 204032	35.2	157.7	307.1	15.09	0.1076	<0.5	–	1.5394	1.7402
LC 201001	58.6	124.9	202.0	7.25	0.0852	n.d.	–	1.5396	1.4687
LC 150009	42.2	116.6	192.0	11.50	0.1113	n.d.	–	1.5394	1.4716
Lactohale®[a]									
LH 207067	56.9	100.3	159.2	4.95	0.1019	n.d.	40.20 (0.7)	1.5379	1.7834
LH 207068	89.6	138.1	206.5	1.54	0.0889	<0.5	40.55 (2.4)	1.5387	2.7653
LH 207069	71.2	112.5	150.2	4.73	0.1344	<0.5	41.51 (1.3)	1.5393	2.6231
LH 207070	79.0	118.4	164.2	1.65	0.0877	n.d.	39.74 (0.7)	1.5394	2.3131
LH 207071	67.3	112.8	163.4	3.05	0.1021	n.d.	40.21 (1.0)	1.5391	1.9675

n.d., not detectable; – not determined.
[a] LH 207067 is produced from LC 115022; LH207068 from LC205037, etc.

at 200 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

3.7. DVS

The amorphous content of the lactose batches as well as the sorption/desorption profiles of the lactoses were determined with a DVS 1 (SMS, London, UK) using a validated method [12] enabling the quantitation of amorphous lactose on the crystal surface as low as 0.5% (w/w).

3.8. Inverse gas chromatography

The surface energy of the inhalation grade lactose was determined by means of an iGC (SMS, London, UK) using pulse iGC at infinite dilution at 30 °C, 0% relative humidity and a helium carrier flow rate of 10 ml/min. Decane, nonane, octane, heptane, toluene, 1,4-dioxane, dichloromethane, ethylacetate and ethanol were used as elutants and detected by means of an FID. The dispersive part of the surface-free energy was calculated by using purpose written iGC software (SMS, London, UK).

3.9. Scanning electron microscopy

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).

3.10. Impinger analysis

The powder blends were aerodynamically assessed with a multistage liquid impinger (MLI) as described in Ph.Eur. [13]. 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. Ten (2.8% powder blends) and 40 (0.25% powder blends) consecutive doses, respectively, 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 approx. 20 mg of the powder blend and 10 (2.8% powder blends) and 20 (0.25% powder blends) capsules, respectively, delivered into the impinger. Samples of all stages, the filter and throat fraction were collected and analysed by means of a validated HPLC method.

4. Results/discussion

4.1. Physico-chemical characteristics of the raw material batches and the resulting inhalation grade lactose

The manufacture of inhalation grade lactose is often tailor-made, i.e. adapted to specific customer requirements, mainly with respect to the average size and the size distribution. To obtain a required particle size distribution the crystallized raw material, in this case the Lactochem® crystals, are fractionated by means of mechanical sieving procedures and by air-classification (Fig. 1). In industrial practice, Lactochem® batches for and the manufacture of inhalation grade lactose is selected to show only small

batch-to-batch variations. However, to be able to estimate effects on the properties of the inhalation grade lactose in case the raw material differs from what is normally used, in this study five batches of Lactochem® were selected which show large differences in terms of average size, size distribution, fines and agglomerate content.

As can be seen from Table 1 the raw material batches vary significantly with respect to their fines content (% < 45 μm by air-jet sieving), the agglomerate content (% > 150 μm determined by sieving), and the size distribution parameters d10%, d50% and d90%. The Lactochem batch 115022 showed a low d10% (28 μm), d50% (97 μm) and d90% (197 μm) whereas batch 204032 had a high d50% and d90% value but still a low d10% value resulting in a high fines content. A third extreme of the raw materials was batch 205037 with high d10%, d50% and d90% values. Accordingly, the BET surface area and the calculated rugosity are different for all the raw material batches which can be attributed to the huge differences in the size distribution data (Table 3). In three of the five batches under investigation, no amorphous content could be measured (no signal at all) whereas two batches contained at least some portion of amorphous area, but clearly below 0.5% (clear signal, but out of calibration

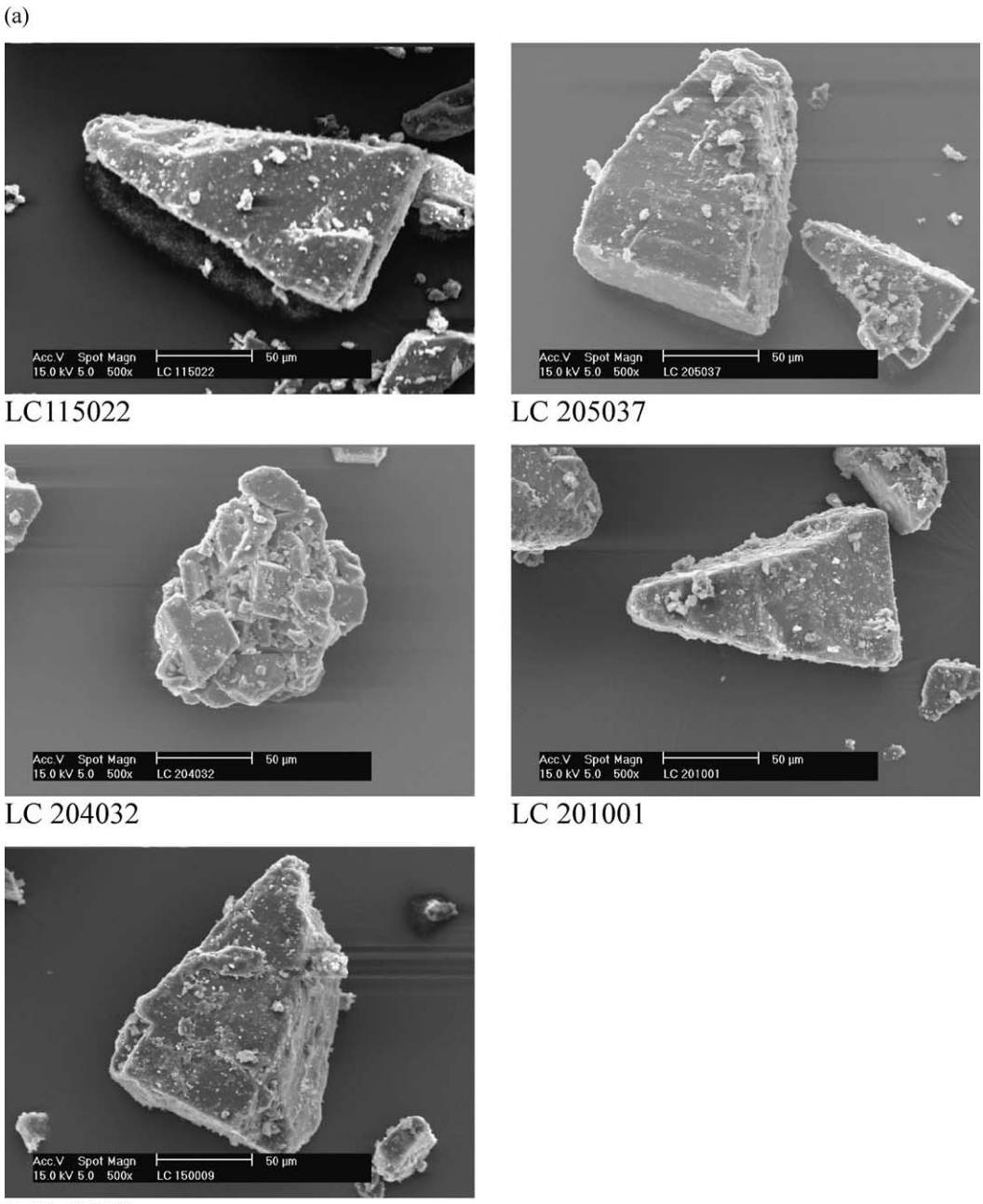

Fig. 2. SEM photographs of (a) the lactose raw materials (Lactochem® crystals) and (b) the final inhalation grade quality.

(b)

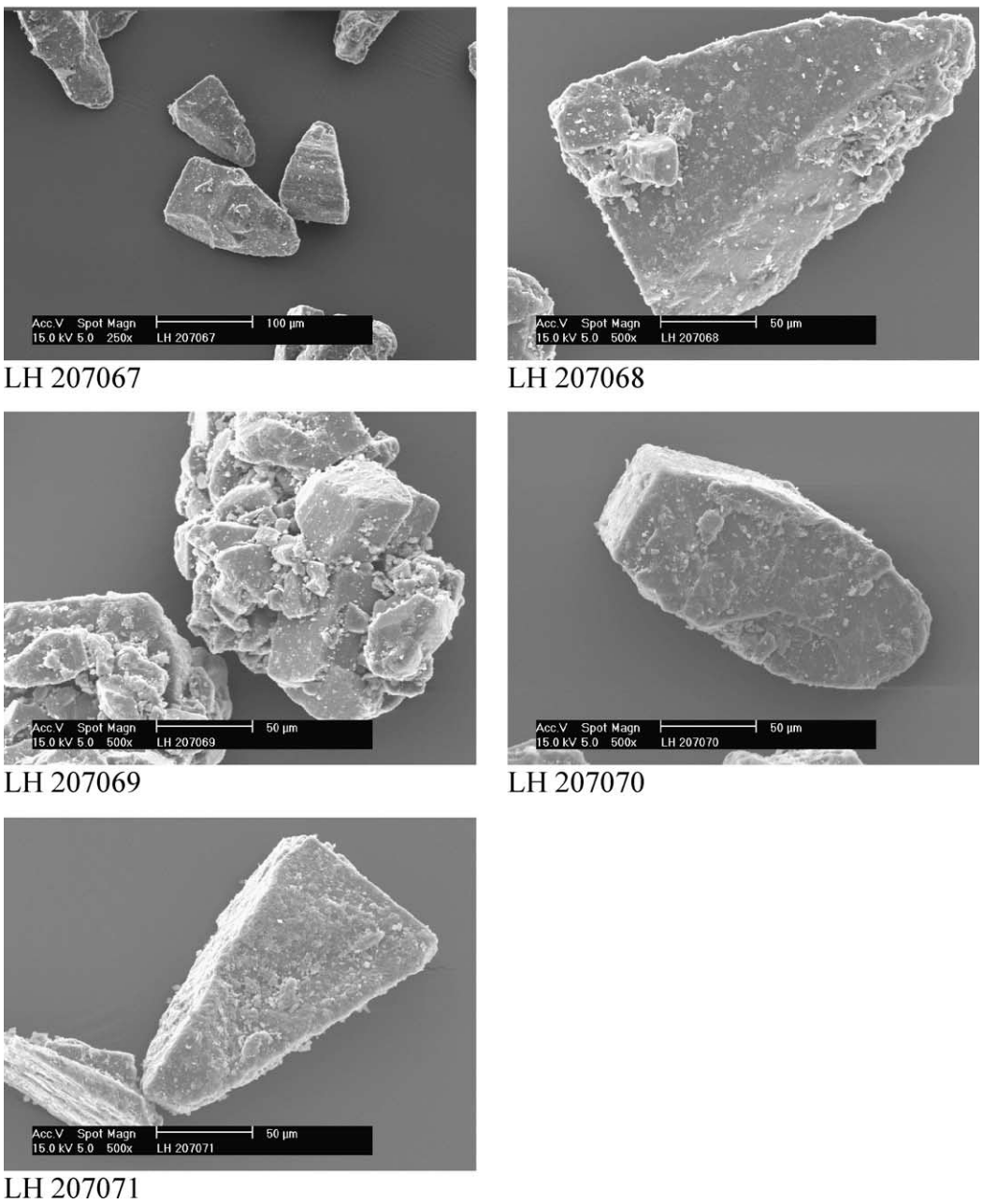

Fig. 2 (*continued*)

range). Looking at the SEM pictures of the raw material lactose batches, Fig. 2a, it can be seen that the batches do not differ with respect to morphology and shape except for batch LC204032 which was an experimental batch of lactose monohydrate and which becomes conspicuous due to its agglomerated character, but still having a very smooth surface texture. It can also be seen from the photographs that the fines content differs between the lactose raw material batches.

Generally, the described physico-chemical attributes of the raw materials were more or less carried over to the inhalation grade material. The batch with the highest d10%, d50%, d90% values resulted in a Lactohale® batch with accordingly high values for these distribution parameters (LH207068). A similar behaviour can be reported for the other batches. The experimental lactose batch LH207069 showed a slightly different size distribution pattern after sieving and air classification. Obviously, a huge amount of large crystal agglomerates were present in the raw material (d90% = 307 μm) which were removed by the sieving and reduced the d90% to 150 μm. Also the VMD was lowered to a higher extent than observed for the other lactose batches. The amorphous content on the surface of the lactose crystals was not influenced by the sieving/air

classification process. This is also supported by the iGC data which show no differences of the dispersive surface energy which is in between 40 and 42 mJ/m^2 for all the produced Lactohale® batches. Also, the specific free energies of desorption (data not shown) were not different between the analysed lactose batches. The SEM pictures reveal that the adhering fines content was effectively removed by the sieving processes so that the Lactohale® batches look very similar, except for the (agglomerated) experimental batch (Fig. 2b).

Finally, also the DSC and XRPD data indicate that the lactose was not affected due to the process conditions. DSC curves and XRPD pattern do not differ at all (data not shown).

4.2. Results of the impinger testing—high drug load (2.8%)

A major focus of the study was the functionality parameter 'fine particle fraction' (FPF) which is defined as the amount of drug particles <5 μm. With an overage of drug (drug-to-carrier ratio 1:36) high FPFs ($>39\%$) were obtained with both devices but, generally, the differences were not statistically different ($P = 0.05$). With the Easyhaler®, Lactohale® batch 207069 showed lower (5%) FPF values; with the Aerolizer®, Lactohale® batches 207067 and 207069 showed slightly lower (5%) FPF values (Table 4). However, a clear relationship between the FPF and any of the physico-chemical parameters determined could not be established. Interestingly, the experimental lactose batch (LH 207069), having the highest surface area and also a high surface roughness and dispersive surface energy, gave the lowest FPF in both devices, even though not statistically significant. This observation is also supported by the shape of the lactose crystals of this batch which appear as agglomerates (Fig. 2b) with hollows and clefts formed by the single lactose crystals. Especially in these clefts, drug particles are accumulated (Fig. 3) and become less entrained during the inhalation. Fig. 4 shows the deposition profile in the MLI. It can be observed that all regular-shaped lactose batches show a high capsule retention whereas the irregular-shaped lactose leads to a distinctly lower retention. This can be explained by the more spherical, but also irregular shape of these lactose crystals resulting in better flowability and air entrainment behaviour. However, a higher amount of drug is deposited on stage 1 of the impinger with this batch.

The fact that the FPF are as high as observed ($>39\%$) is attributed to the drug overage as well. An overage of drug leads to adhesion of drug particles to those crystal surfaces with the highest surface energy with a huge proportion of drug being adhered to the low energy sites of the drug crystals [14].

In summary, there is no obvious relationship between the functionality of the DPI lactose batches and the investigated physico-chemical parameters at the high drug load.

4.3. Results of the impinger testing—low drug load (0.25%)

The MLI results of the SBS/lactose blends with low drug load were significantly different from the results of the first part of the study. The FPFs were generally lower in all cases as assumed according to the 'hot spot theory' (a high drug load in the mix occupies the active sites on the lactose surface and enables the remaining drug particles adhering at the low energy sites to be easily detached, whereas in the case of the second part of the study the selected drug concentration was much lower so that the drug is bound more strongly to the lactose crystals). This is also supported by the SEM photographs (Fig. 3) which reveal that the surface coverage of the lactose crystals with drug particles is reduced as compared to the mixes with the 10-fold drug concentration. Dickhoff et al. [15] recently reported similar findings where the drug retention on the carrier is decreasing with increasing carrier payloads.

The FPFs ranged from 12 to 27% with the Aerolizer® device and from 15 to 31% in case of the Easyhaler® device (Table 5). The FPF values obtained with the Easyhaler® were generally higher than with the Aerolizer® device, except for batch LH207067 (Figs. 5 and 6). Again, the irregular shaped lactose resulted in the lowest device retention in the Aerolizer® but then deposits the drug also on stage 1 of the impinger. It is the batch LH207067, which was produced from the aged material that resulted in the lowest FPF with both devices. Batches LH207069 (the irregular shaped lactose) and LH207070 differed not significantly ($P = 0.05$) from the aged batch when

Table 4
Aerodynamic properties of the SBS/lactose blends (drug-to-carrier ratio 1:36) with the Aerolizer® and the Easyhaler® device (SD)

Batch no.	Aerolizer®			Easyhaler®		
	% <5 μm	MMAD (μm)	GSD (μm)	% <5 μm	MMAD (μm)	GSD (μm)
LH 207067	39.2 (3.1)	3.11 (0.02)	1.98 (0.07)	46.8 (3.5)	2.81 (0.06)	1.83 (0.09)
LH 207068	47.3 (0.5)	2.87 (0.04)	1.92 (0.03)	44.5 (3.6)	2.88 (0.24)	1.92 (0.06)
LH 207069	40.9 (1.8)	3.11 (0.03)	1.95 (0.02)	39.4 (1.6)	2.98 (0.05)	1.94 (0.02)
LH 207070	46.5 (3.6)	2.99 (0.11)	1.96 (0.05)	47.0 (1.4)	2.81 (0.10)	1.89 (0.03)
LH 207071	44.0 (1.3)	2.88 (0.02)	1.97 (0.03)	49.1 (3.6)	2.79 (0.02)	1.88 (0.08)

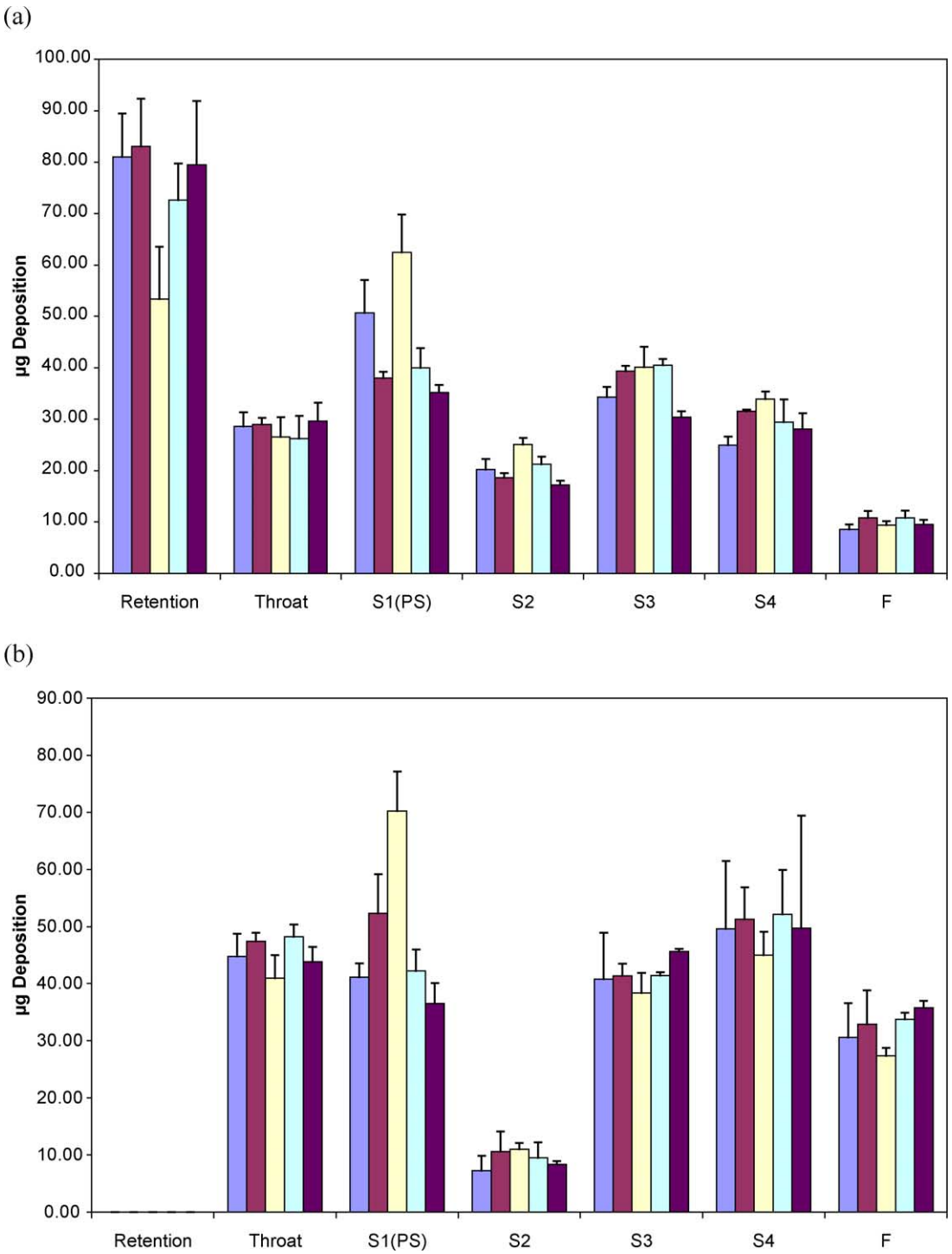

Fig. 3. Deposition pattern of salbutamole sulphate blends in the Multistage Liquid Impinger with (a) the Aerolizer device and (b) the Easyhaler device.

the Aerolizer® is used for aerosolization but resulted in higher FPF values when the Easyhaler® is used for delivery. The best results were obtained with batch LH207068 and LH207071 with both devices (Table 5, Fig. 6). Interestingly, the same trend with respect to the FPF could be observed for both devices, i.e. batches showing poor dispersibility with the Aerolizer® perform similar with the Easyhaler®, although on a lower level. The fact that the Easyhaler® showed better results with respect to the FPF could be explained by the lower airflow used to entrain the particles. A higher airflow results in a higher deposition rate on the upper stages of the impinger, especially stage 1, and accordingly to less deposition in stages 3, 4 and filter (Fig. 5). Even though significant differences were observed between all the different batches of lactose (which should be fairly similar because they all comply with the specification

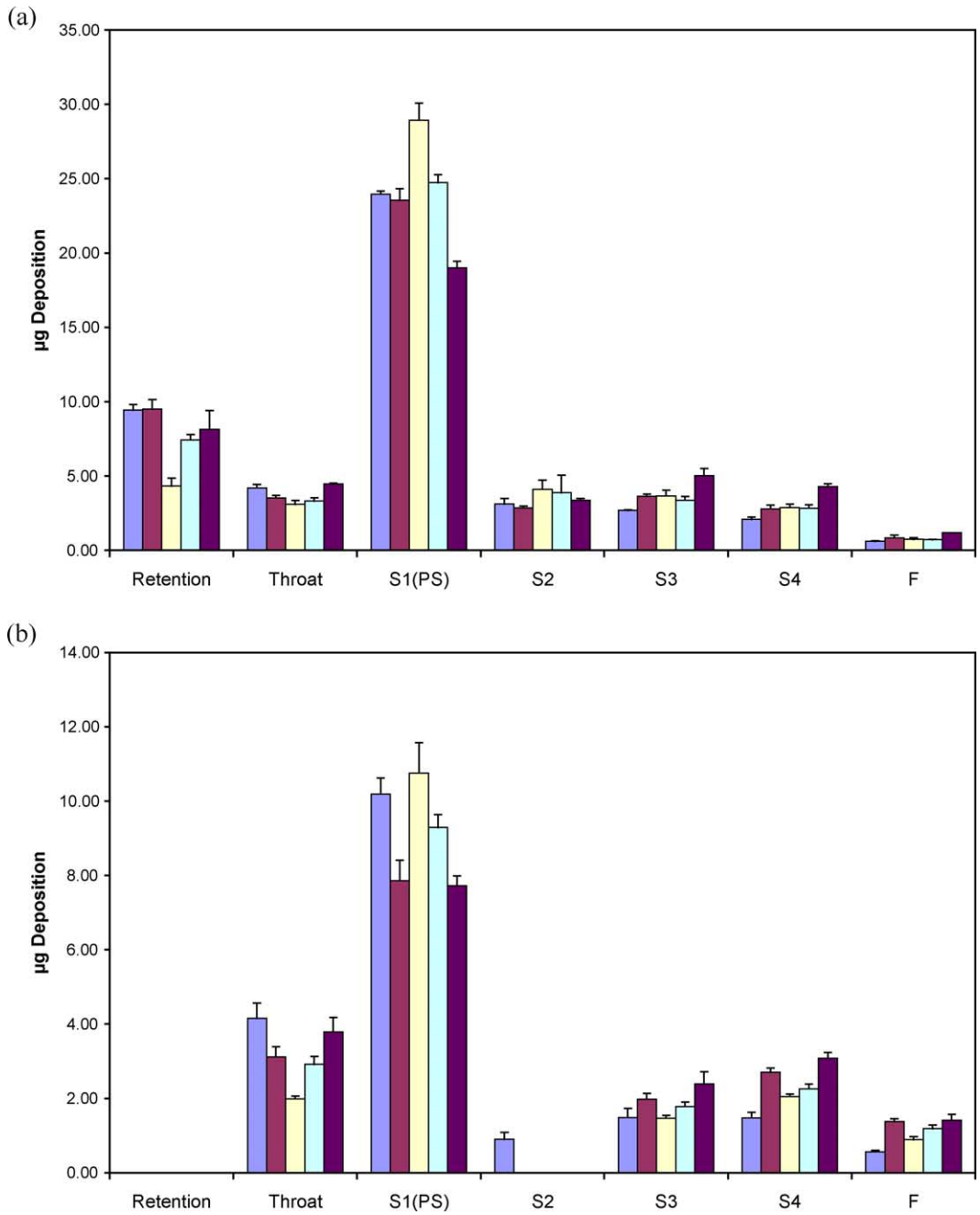

Fig. 4. Deposition pattern of salbutamol sulphate blends (low drug load) in the multistage liquid impinger with (a) the Aerolizer device and (b) the Easyhaler device.

Table 5
Aerodynamic properties of the SBS/lactose blends (drug-to-carrier ratio 1:400) with the Aerolizer® and the Easyhaler® device (SD)

Batch no.	Aerolizer®			Easyhaler®		
	% < 5 μm	MMAD (μm)	GSD (μm)	% < 5 (μm)	MMAD (μm)	GSD (μm)
LH 207067	14.1 (0.3)	3.88 (0.12)	2.17 (0.04)	14.9 (1.5)	3.93 (0.31)	2.03 (0.07)
LH 207068	18.9 (1.5)	3.37 (0.11)	2.04 (0.04)	29.8 (0.6)	2.48 (0.02)	1.29 (0.01)
LH 207069	16.2 (1.6)	3.85 (0.29)	2.11 (0.04)	21.5 (1.2)	2.52 (0.03)	1.29 (0.01)
LH 207070	17.3 (0.5)	3.78 (0.35)	2.11 (0.05)	25.0 (1.1)	2.49 (0.03)	1.29 (0.01)
LH 207071	27.2 (1.1)	3.16 (0.02)	1.97 (0.03)	31.0 (0.5)	2.52 (0.03)	1.28 (0.01)

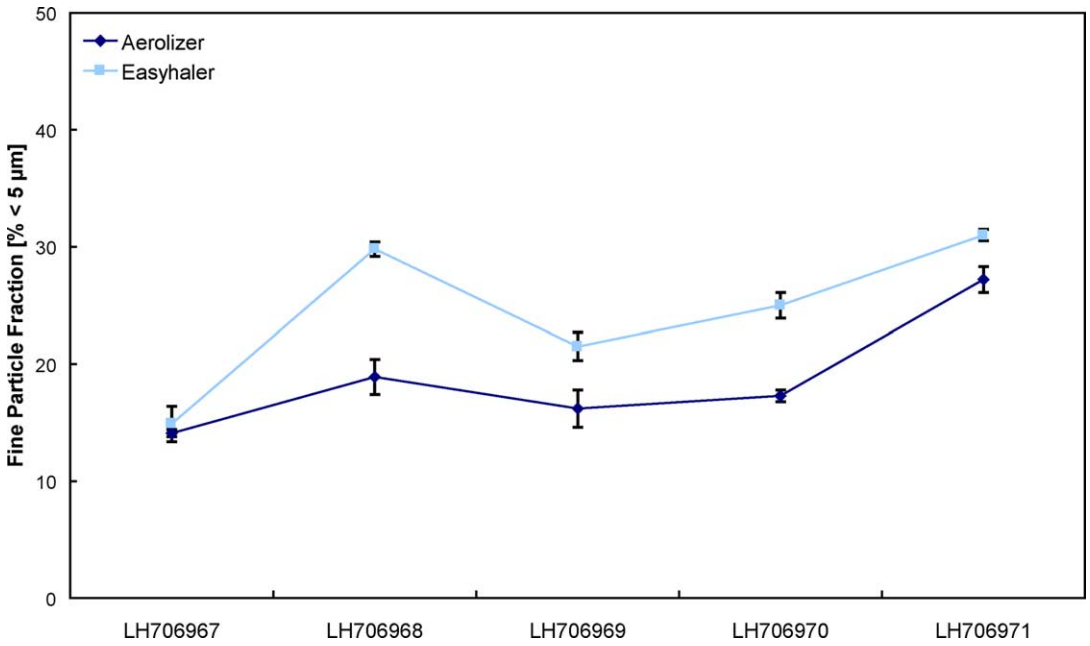

Fig. 5. Fine particle fractions (% < 5 μm) of the SBS/lactose blends with low drug load (0.25%).

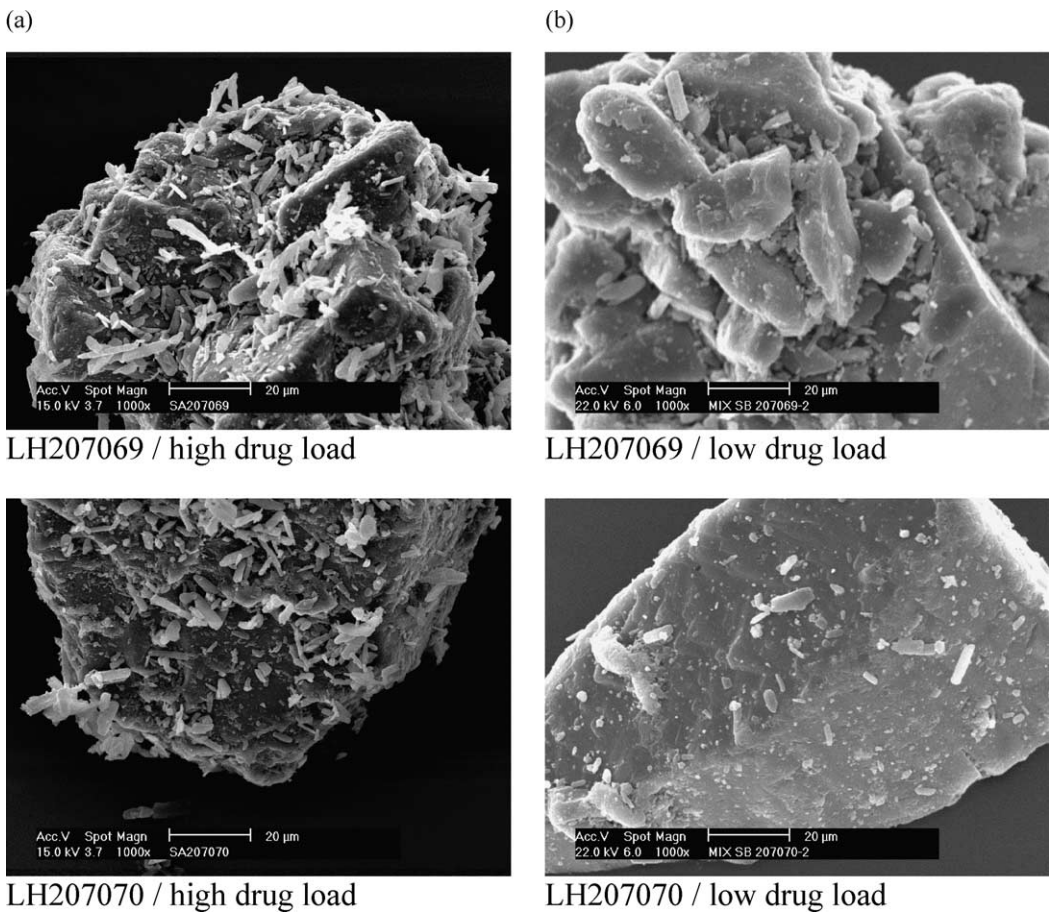

Fig. 6. SEM photographs of SBS/lactose blends with (a) high and (b) low drug load; blends with batches LH207067 and LH207070 were selected exemplarily.

of inhalation grade lactose), these differences could not be linked to differences in the raw material or in the physico-chemical characteristics of both the raw material and the resulting inhalation grade lactose. By trend, the Lactohale® batches with a high d50% and d90% showed better performance than the batches with smaller average particle size. Also by trend, batches with lower content of small lactose particles (% $< 45\ \mu m$) seem to show better performance. This becomes especially clear with the high dose formulation in the Aerolizer®. This observed trend is somewhat in opposition to data published in the literature and earlier experience where it is claimed that the dispersibility of inhalation powders, expressed as % FPF, could be enhanced by using a fine lactose quality or by the addition of fines [9]. However, it must be acknowledged that most of these published studies were done with an excess of drug, in most cases $>1\%$ drug concentration in the powder blends.

5. Conclusions

This study was undertaken to find out whether there is a physico-chemical parameter of the lactose that can predict the efficacy of an inhalation powder produced. It has been demonstrated by this study that the batch variations of the batches under investigation could result in significant differences of the properties of the inhalation powders manufactured with these batches. This is not as relevant for powder blends using a high drug-to-lactose ratio but is very relevant for those drug blends containing a low amount of drug.

This study shows the importance of small batch-to-batch variations in the particle size distributions of the raw material lactose used for further processing to inhalation grade lactose.

References

[1] S.J. Smith, A. Bernstein, Therapeutic uses of lung aerosols, in: A.J. Hickey (Ed.), Inhalation Aerosols, Marcel Dekker, New York, 1996, pp. 233–269.
[2] C. Winneps, DPIs in the ascent—changes in the market, Management Forum Conference on Recent Developments in Dry Powder inhalers, London, 2003.
[3] H. Steckel, Inhalationspulver—Neuere Entwicklungen bei Pulverinhalatoren, PZ Prisma 3 (2003) 145–157.
[4] D.A. Wall, Pulmonary absorption of peptides and proteins, Drug Deliv. 2 (1995) 1–20.
[5] H. Lahrib, X.M. Zeng, G.P. Martin, C. Marriott, J. Pritchard, The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate, Int. J. Pharm. 191 (1999) 1–14.
[6] H. Steckel, Inhalation powders—a simple dosage form for pulmonary delivery? Swiss Pharma 9a (2002) 15–28.
[7] D.L. French, D.A. Edwards, R.W. Niven, The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation, J. Aerosol Sci. 27 (1996) 769–783.
[8] J.N. Staniforth, Improvement in dry powder inhaler performance: surface passivation effects, Aerosol Sci. Technol. 22 (1995) 346–353.
[9] P. Lucas, M.J. Clarke, K. Anderson, M.J. Tobyn, J.N. Staniforth, The role of fine particle excipients in pharmaceutical dry powder aerosols, Respir. Drug Deliv. VI (1998) 243–250.
[10] D. Ganderton, N.M. Kassem, Int. Patent Application, WO 91/11179, 1991.
[11] X.M. Zeng, G.P. Martin, C. Marriott, J. Pritchard, The use of lactose recrystallised from carbopol gels as a carrier for aerosolized salbutamol sulphate, Eur. J. Pharm. Biopharm. 51 (2001) 55–62.
[12] P. Markefka, H. Steckel, Assessment of low levels of amorphous content in lactose by DVS and isothermal microcalorimetry, Arch. Pharm. Med. Chem. 335 (Suppl 2) (2002).
[13] European Pharmacopoeia, 3rd supplement, 2.9.18, 2001.
[14] H. Steckel, N. Bolzen, The effect of drug concentration and addition of a ternary agent on the fine particle fraction of powder mixtures for inhalation, Int. J. Pharm., Submitted for publication, 2004.
[15] B.H.J. Dickhoff, A.H. de Boer, D. Lambregts, H.W. Frijlink, The effect of carrier surface and bulk properties on drug particle detachment from crystalline lactose carrier particles during inhalation, as function of carrier payload and mixing time, Eur. J. Pharm. Biopharm. 56 (2003) 291–302.