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Influence of fine lactose and magnesium stearate on low dose dry powder inhaler formulations

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Abstract

The behaviour of dry powder blends for inhalation, depending on the amount of fine lactose particles smaller than 10 μm and the presence of magnesium stearate (MgSt), was studied in this work. A laser light diffraction method was developed to determine accurately size and volume fraction of these fine lactose particles in coarse carrier lactose ($x_{50} \sim 220$ μm). A linear relationship between measured volume fraction undersize at 10 μm Q_3(10 μm) and added fine lactose could be established. Aerodynamic particle size distribution analysis of lactose showed that the fine lactose was attached to the coarse particles. In the presence of MgSt this interaction was increased. Consequently, the number of free active sites on the carrier surface was reduced and the investigated drug (formoterol fumarate dihydrate) was more effectively delivered. Addition of fine lactose and MgSt improved the aerodynamic performance the drug, as determined by resulting fine particle fraction, by 3% (for each 1% of added fine lactose) and 10%, respectively. Stability tests indicated that added MgSt was the most relevant of the studied parameter to achieve a stable aerodynamic performance. Its ability to protect the moisture uptake into the system was considered as rational for this effect.

Keywords: Formoterol; DPI; Inhalation; Lactose; Magnesium stearate

1. Introduction

Ensuring development and manufacture of effective, reliable and robust drug products is a major objective of pharmaceutical companies. Over recent years it became apparent that inhalation products and specifically dry powder inhaler (DPI) formulations present multiple challenges during development to achieve this goal. A large number of contributing factors to the performance of a DPI system have been studied. However, there is a mutual agreement in the scientific community that parameters closely linked to particle–particle interactions are the main contributors to the behaviour of DPIs as characterised by the aerodynamic particle size distribution (French et al., 1996; Vanbever et al., 1999; Tong et al., 2006).

DPIs commonly consist of a carrier material (alpha-lactose monohydrate), ensuring flowability, reducing agglomeration and providing bulk to make handling and dosing possible, and a relative low amount (0.05–10%) of active pharmaceutical ingredient (API) with particle size typically below 10 μm. Furthermore, some advanced products have been formulated using a ternary agent such as magnesium stearate (MgSt) (Young et al., 2002; Mueller-Walz et al., 2006). However, even this small number of formulation components potentially possesses a wide variability in terms surface characteristics that, in turn, influences parameters such as contact area, and energetic situation on the surface. The energetic situation governs polar and apolar interactions, the influence of humidity, electrostatics and a number of other interactions. Contact area, on the other hand, provides the ground for these interactions to result in forces, acting between particles.

Fine lactose particles in the same size range as the API have been pointed out as key component in this system of forces to improve the formulation performance (Zeng et al., 1998). One of the present hypotheses to explain this phenomenon is based on the presence of active sites and the agglomeration of drug and fine excipient (Jones and Price, 2006). Active sites are interpreted as locations of disturbance on the surface of a crystal were more active molecular groups are presented to the outside. This might be due to simple dislocations in the crystal lattice,

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or the complete distortion of the molecular order. Such regions might have different depth but in every case present areas of higher surface interaction compared with the surrounding crystal areas. The presented paper deals with the influence of fine lactose particles, which can be present in the carrier and resulting in variation in surface and contact area, on the performance of dry powder inhaler formulations. A highly sensitive laser light diffraction method was developed to analyse small variations in the particle size distribution of the carrier. The method was carefully qualified with respect to sample preparation, dispersing conditions and sensitivity.

Although the influence of carriers on the performance of DPI formulations has already been demonstrated in various publications, there is a lack in available literature concerning not only the particle size of the carrier measured by laser light diffraction but also the aerodynamic particle size distribution. The result of these kinds of investigations is likely to be of relevance in gaining better insight into the modelling of the discussed systems. This problem will be addressed in the presented work.

An inhalation product such as a DPI formulation needs to have a stable aerodynamic performance during its designated shelf life to become a commercial product. Moisture has been identified as an important factor for decreasing performance over time (Maggi et al., 1999; Bérard et al., 2002; Price et al., 2002; Young and Price, 2004). It can act as plasticizing agent, changing the surface of the particles and promoting strong adhesion or agglomeration.

Formulations with a low concentration of active substance (such as the formulation studied in this work) are more influenced by the properties of the carrier. This might be associated with the number and availability of active sites on the carrier. In fact, Young et al. (2005) showed that formulations with an active concentration between 0.02 and 0.27% (m/m), deliver about the same fine particle dose (FPD). This observation was explained by the assumption that only after the saturation of active sites a linear increase of the delivered dose with the active concentration is observed (Young and Price, 2006). Therefore, slight variation in present active sides on the carrier (e.g. by changes in manufacturing procedures) might have a significant influence. This work attempts to further elucidate this mechanism.

For this work, the composition of carrier was varied, by changing the amount of fine lactose particles, and by changing the ratio of available surfaces from one carrier substance (lactose) to a controlled mixture of a main carrier and a ternary agent (magnesium stearate). The influence of these changes on the performance of the dry powder inhaler formulation was investigated using a formulation similar to Foradil® Certihaler™ (Novartis Pharma AG CH-Basel, formulation technology and inhaler device developed by SkyePharma AG, CH-Muttenz).

2. Materials and methods

2.1. Materials

Formoterol fumarate dihydrate (formoterol fumarate, FF) was supplied by Novartis Pharma AG (Switzerland), coarse α-lactose monohydrate of pharmaceutical grade (Respitose SV001, $x_{50} = 220\,\mu m$) by DMV International (Veghel, The Netherlands), micronised α-lactose monohydrate ($x_{50} = 5\,\mu m$) by Borculo-Domo (Zwolle, The Netherlands) (also referred to as 'fine lactose' in the following text) and inhalation grade magnesium stearate by Peter Greven (Germany).

Isopropanol, methanol, acetonitrile, glacial acetic acid, perchloric acid were purchased from Merck (Germany) and sodium hydroxide, as 50% solution in water, from Fluka (Switzerland). Deionised water (18 MΩ) was obtained by a MilliQ RG water purification system.

2.2. Blend preparation

Lactose pre-blends containing Respitose and different amounts of fine lactose were prepared as 20 g batches by tumble blending (Turbula mixer, Willy A. Bachofen AG, Switzerland) at 32 rpm for 20 min. The same process was used to obtain lactose–magnesium stearate (0.5%, m/m) pre-blends. Therefore, pre-blends with and without magnesium stearate were mixed following the same procedure. Final blends of FF (0.22%, m/m) with pre-blends were prepared by the same process.

2.3. Laser light diffraction measurements

Laser light diffraction (LLD) analysis was performed using a Sympatec HELOS (Sympatec GmbH, Germany) equipped with a 500 mm lens and a wet dispersion unit (QUIXEL). Pump speed and ultrasonication time, if not further specified, were set at 20% and 60 s, respectively. Isopropanol was used as suspension medium, saturated with lactose and filtered through a 0.1 μm filter. The optical concentration during testing was between 10 and 20%. Data acquisition and calculation was performed by Windox 4 using Fraunhofer theory.

2.4. Aerodynamic particle size distribution

The aerodynamic particle size distribution (APSD) was determined using an eight-stage Andersen Cascade Impactor (ACI) with pre-separator (Copley, UK) operating at an airflow rate of 60 L/min. The impaction plates were coated with a 1% (v/v) solution of Tween 20 (Serva, Germany) in methanol to prevent particle bounce and re-entrainment. The Certihaler (SkyePharma, Switzerland) was used as inhalation device. The powder formulation (560 mg) was filled into the reservoir of the device, which was subsequently assembled with the device body. Ten actuations were discharged at a flow rate of 60 L/min (for 4 s) for each measurement. The amount of FF and lactose deposited in the inhaler, throat, pre-separator, on the individual impactor plates, and stage walls were quantified by HPLC.

The fine particle fraction (FPF) was calculated from the amount of FF with aerodynamic size lower than 4.6 μm divided by total mass recovered. One replicate was performed.

2.5. HPLC analysis of formoterol fumarate

Formoterol fumarate (FF) was analysed by HPLC employing acetic acid (0.5 mol/L) as solvent and a mixture of perchloric

acid solution pH 3.5 and 27% (v/v) acetonitrile as mobile phase running at a flow rate of 1.0 mL/min. The HPLC system consisted of an Agilent 1100 system (Agilent Technologies, USA) with a 125 mm, 4.6 mm i.d. column packed with 5 μm C-18 HD (Nucleosil 100, Macherey-Nagel AG, Switzerland). Detection was performed at 220 nm and the retention time for FF was about 5.5 min.

2.6. HPLC analysis of lactose

Lactose was analysed by HPLC employing a mixture of methanol and water (20/80, v/v) as solvent and a NaOH solution (0.1 mol/L) as mobile phase running at a flow rate of 1.0 mL/min. The HPLC system consisted of an Agilent 1100 system (Agilent Technologies, USA) with a 250 mm, 4 mm i.d. column packed with 10 μm Resin (CarboPac PA10, Dionex, USA) and an electrochemical detector (ED50A, Dionex, USA). The retention time for lactose was about 10 min.

3. Results and discussion

3.1. Determination of fine particles in the carrier lactose by laser light diffraction

The particle size distribution (PSD) of the carrier lactose, especially the fine lactose particles below 10 μm, has a significant influence on the performance of a DPI formulation (Zeng et al., 1998). Therefore, the first objective of the present study was to establish a particle sizing method to quantify the amount of these fine particles in the carrier lactose, where typically more than 90 vol% of the particles are within 100 and 500 μm. One obstacle to overcome in order to obtain a true representation of the particle size distribution is the cohesion between the particles. Based on the Johnson–Kendal–Roberts model (Johnson et al., 1971) the interaction between two particles can be reduced by dispersing the material in a suitable non-solvent. Isopropanol has been chosen as dispersion liquid.

As lactose is not completely insoluble in isopropanol a saturated solution was prepared. The suitability of this approach was confirmed by a consistent size distribution in the suspension over a period of 30 min.

The two main method related parameters of the wet dispersion system are pump speed and ultrasonication time. If the speed power is too small larger particles might settle within the system, whereas a set-up above the suitable limit can introduce air bubbles into the system. The ultrasonication time influences the de-agglomeration process. If the time is too short, the de-agglomeration might not be sufficient. On the other hand, particle comminution might lead to an overestimation of the fine grain as result of a long ultrasonication time (Lu et al., 2002). The influence of these parameters was determined by a factorial design experiment 2^2 [ultrasonication time (60 and 480 s) and pump speed (20 and 40%)]. The response variable was the volume fraction undersize at 10 μm [Q_3(10 μm)]. Results are shown in Table 1. Values of pump speed (p) and ultrasonication time (u) were scaled to $x_1 = (p - 30)/10$ and $x_2 = (u - 270)/210$. The influences of the pump speed parameter (x_1), ultrasonication time parameter (x_2) and the synergism (x_1x_2) were determined as shown in Eq. (1) (dimensionless values)

Table 1
Q_3(10 μm) (%, v/v) obtained by the factorial design experiments

Pump speed (%)	Ultrasonication time	
	60 s	480 s
20	2.27	4.39
40	2.28	5.67

$$Q_3(10\,\text{mm}) = 3.6525 + 0.3225x_1 + 1.3775x_2 + 0.3175x_1x_2 \quad (1)$$

The results showed no significant influence of the pump speed and synergism with ultrasonication time in the observed range. A constant set-up of 20% pump speed was chosen for the following investigation.

As the ultrasonication time (x_2) showed a significant influence on the measured Q_3(10 μm) values, the influence has been studied in more detail: samples with different amounts of fine lactose were analysed after 0, 30, 60, 120, 240 and 480 s of ultrasonication time.

Analysing un-blended fine lactose, the ultrasonication test series resulted in constant particle size distributions after 60 s ultrasonication. Therefore, the de-agglomeration of fine lactose was completed at this time point. However, if coarse lactose was present in the sample, Q_3(10 μm) increased throughout the ultrasonication test series by about 1.5% (v/v) every 60 s. This observation indicates comminution of coarse particles. Consequently, the optimal balance between de-agglomeration and undamaged particles was found to be 60 s.

Sixteen blends, covering the whole range from 0 to 100% (m/m) of fine lactose, were analysed to study the relationship between the amount of fine lactose and measured Q_3(10 μm) values.

The PSD of a selected number of blends can be seen in Fig. 1. The obtained values ranged between Q_3(10 μm) = 2.5% (v/v) for

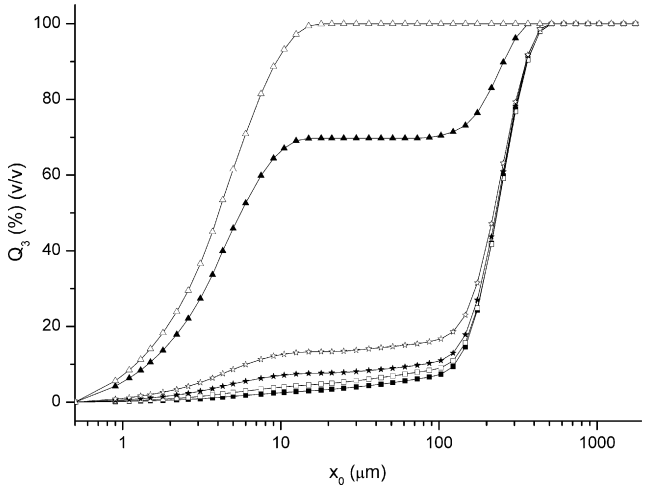

Fig. 1. Particle size distribution of lactose: lactose as supplied (■), samples with added fine lactose 1% (□), 5% (⋆), 10% (☆) and 50% (▲) of fine lactose; fine lactose (△).

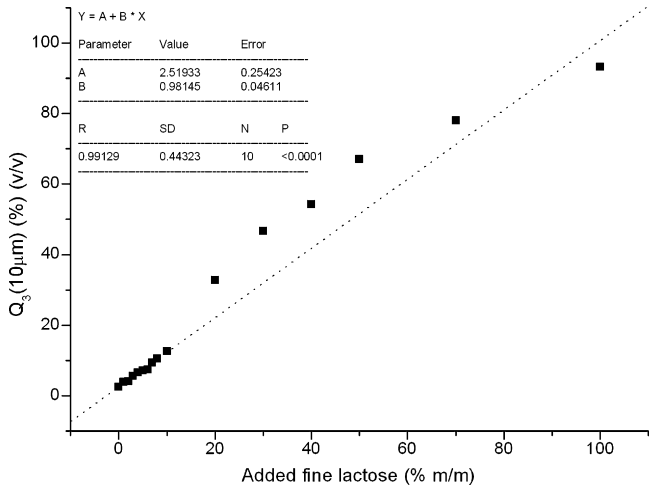

Fig. 2. Volume fraction undersize at 10 μm (Q_3(10 μm)) of lactose blends measured by LLD plotted against the amount of added fine lactose. The curve was calculated by linear regression of the points below 10% fine lactose, inclusive.

pure carrier lactose (Respitose) and up to $Q_3(10\,\mu m) = 93\%$ (v/v) for pure fine lactose. $Q_3(10\,\mu m)$ values were plotted against amount of fine lactose in Fig. 2. This figure shows a linear relationship up to 10% (m/m) of added fine lactose. The linear regression between $Q_3(10\,\mu m)$ and the amount of fine lactose was calculated as

$$Q_3(10\,\mu m) = 0.981a + 2.519, \quad R^2 = 0.9827 \qquad (2)$$

The slope of 0.981 shows a very good agreement with the expected value (each 1% (m/m) of fine lactose increases the $Q_3(10\,\mu m)$ value by 0.98% (v/v) what is close to the expected 0.93% (v/v)). The *y*-intercept of 2.519 corresponds to $Q_3(10\,\mu m) = 2.5\%$ (v/v) of pure carrier lactose (Respitose). The obtained standard deviation of the regression line was S.D. = 0.443, yielding a measure for the precision of the method of ±0.4% (v/v).

Above the 10% (m/m)-threshold, $Q_3(10\,\mu m)$ values were greater than expected. This deviation from linearity was possibly caused by the extremely broad particle size distributions (1–500 μm) for the following reason: The intensity of light, scattered by equal mass of particles, decreases with increasing particle size. This can yield an underestimation of the coarse particles in the presence of much more intensely scattering fine particles. However, as will be shown below, the interesting blending range was only up to 10% (m/m) of added fine lactose. In this range of $2\% < Q_3(10\,\mu m) < 15\%$ (v/v) the response of the method was linear and the $Q_3(10\,\mu m)$ values could be accurately determined within an error of ±0.4% (v/v).

3.2. Influence of fine lactose and magnesium stearate on aerodynamic performance

3.2.1. Initial tests

FF blends were prepared with different amounts of fine lactose and MgSt (see Table 2) and filled into the reservoir of the Certihaler device. The APSD of these samples was determined by Andersen Cascade Impactor (ACI).

Table 2
Composition of the formoterol fumarate blends

Sample	Fine lactose (%, m/m)	MgSt 0.5% (m/m)
FSG00	0	N
FSG01	1	N
FSG02	2	N
FSG03	3	N
FSG04	4	N
FSG05	5	N
FSG06	10	N
FMG00	0	Y
FMG01	1	Y
FMG02	2	Y
FMG03	3	Y
FMG04	4	Y
FMG05	5	Y
FMG06	10	Y

A potential variation in metered weight and, consequently, in the total amount of recovered drug was expected, based on the slight variation in powder bulk density as a result of the different blend composition and the volume-defined metering of the device. However, this phenomenon was not observed in this study with the average of total drug recovery for all tested blends being almost constant.

The fine particle fraction (FPF) of FF (particles between 0.4 and 4.6 μm), calculated as a percentage of total recovery, is shown in Fig. 3. The FPF increases with the amount of added fine lactose. This influence appears to be linear for up to 5% of fine lactose, with an increase of about 3% for each percent of added fine lactose. This observation is in agreement with the theory of unsaturated active sites on the carrier. The more fine lactose is introduced into the system the smaller the interaction between carrier and drug and the higher the likelihood to form smaller agglomerates between drug and fine lactose and, consequently, the greater the amount of liberated drug substance.

The result for 10% of added fine lactose deviated from the apparently linear relationship by showing a similar behaviour as the formulation containing 5% of fine lactose. It might be assumed that above 5% of fine lactose the mechanism of influ-

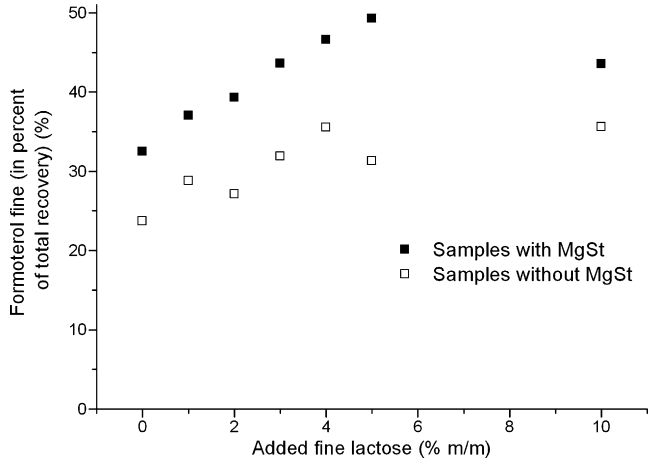

Fig. 3. Formoterol fumarate fine particle fraction of total recovery vs. amount of added lactose.

ence on the performance undergoes a change. Competing effects such as the saturation of activated areas on the carrier surface (Young et al., 2005) or the formation of drug–fines agglomerates for easier lift-off (Begat et al., 2004; Louey and Stewart, 2002) could offer an explanation for this behaviour. However, no conclusive explanation can be given at this point.

Adding MgSt to the formulation also increased the FPF (see Fig. 3). The tested amount of 0.5% (m/m) increased the FPF by about 10% on average for all blends. Fig. 3 also shows a better linear fit for samples with MgSt compared to samples without MgSt, which is a positive observation in terms of predictability of formulation behaviour.

The APSD of FF of four samples with and without MgSt is shown in Fig. 4. There were apparent differences in the distribution depending on the addition of MgSt. The amount of FF retained in adaptor and throat was in direct correlation with the amount of fine lactose in samples without MgSt. With an increased amount of fine lactose the FPF of FF was also increased. Powder blends with MgSt showed a stable deposition in the throat close to the value achieved by formulations without MgSt and 4% (m/m) of added fine lactose. Again this can be explained by the active sites model (Kawashima et al., 1998): If a higher amount of fine lactose is present in the formulation, the probability for them to adhere to the active coarse lactose sites is higher. This possibly leaves free formoterol fumarate to agglomerate and be retained in the throat. MgSt has a higher affinity to lactose (no electrostatic repulsion) (Lachiver et al., 2006). Therefore, active sites could potentially be more readily occupied which, in turn, might explain why the blend containing 0.5% (m/m) of MgSt shows throat retention results similar to blends with 4% (m/m) of fine lactose.

In terms of retention in the pre-separator, there was an inverse relationship between the amount of fine lactose and amount of retained FF: With an increase of added fine lactose the retained drug was decreased. The presence of MgSt further decreased the amount of retained FF. Similarly to the behaviour described above, this fits in the active sites and fine agglomerates models as most of the large lactose carrier particles are trapped in the pre-separator. If the amount of added fine lactose, whether it being lactose or MgSt, is increased, the actives sites are covered and more "free" active drug is available. Regarding the agglomeration model, the increased presence of fine lactose increases the likelihood for agglomerates and a concomitant reduction of retained drug on the large lactose carrier.

The deposition of FF in the APSD range of 8.7–4.6 μm was not significantly influenced by the amount of added fine lactose. The values for formulations with MgSt were only slightly lower than the ones without MgSt.

In terms of FPF (particles between 0.4 and 4.6 μm), there was a clear difference in pattern between blends with and without MgSt. Both series of formulations led to a major deposition of FF in the size range between 3.2 and 2.0 μm (between 12.5 and 17.5% for samples with MgSt and between 10 and 15% for samples without). However, samples with MgSt resulted in a higher recovery in the size range between 2.0 and 1.1 μm whereas samples without MgSt showed a similar deposition as for the range between 3.2 and 2.0 μm. This resulted in a smaller mass median aerodynamic diameter (MMAD) for formulations with MgSt.

The APSD of lactose of these samples was determined and is shown in Fig. 5a and b. The majority of lactose particles (laser light diffraction showed x_{50} of about 220 μm) were retained in the pre-separator. An unexpected phenomenon was observed in the form of an increase in retained lactose in the pre-separator with an increase of added fine lactose. This behaviour is in opposite to the result for FF, but again proof for the validity of the active sites model: active sites can be filled with fine lactose, MgSt or FF. With an increase of fine lactose, the probability of interaction between coarse and fine lactose is also increased. Therefore, more lactose is retained in the pre-separator. Besides its effect as fine particles, MgSt reduces the electrostatic repulsion between lactose particles and, consequently, increases the attachment of fine lactose to the coarse carrier even further. This is confirmed in Fig. 5 which shows that in samples with MgSt

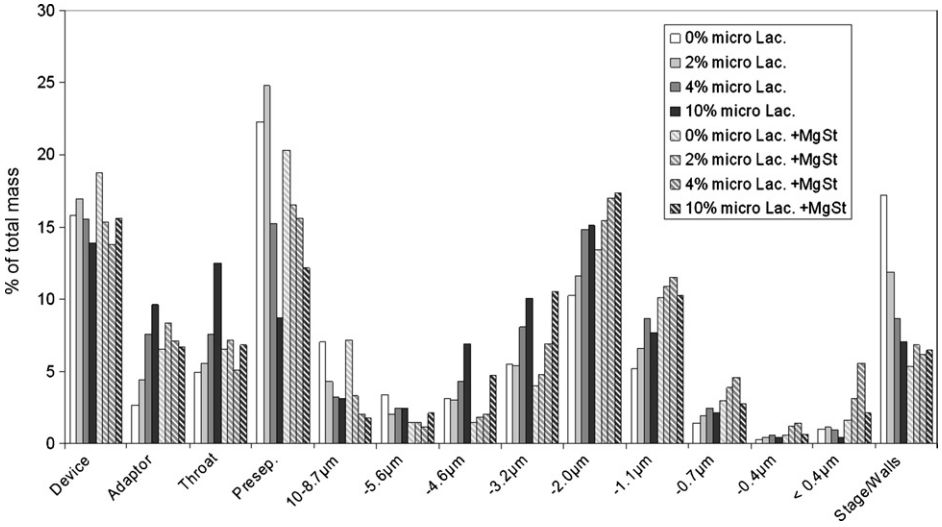

Fig. 4. Aerodynamic particle size distribution of formoterol fumarate (initial time).

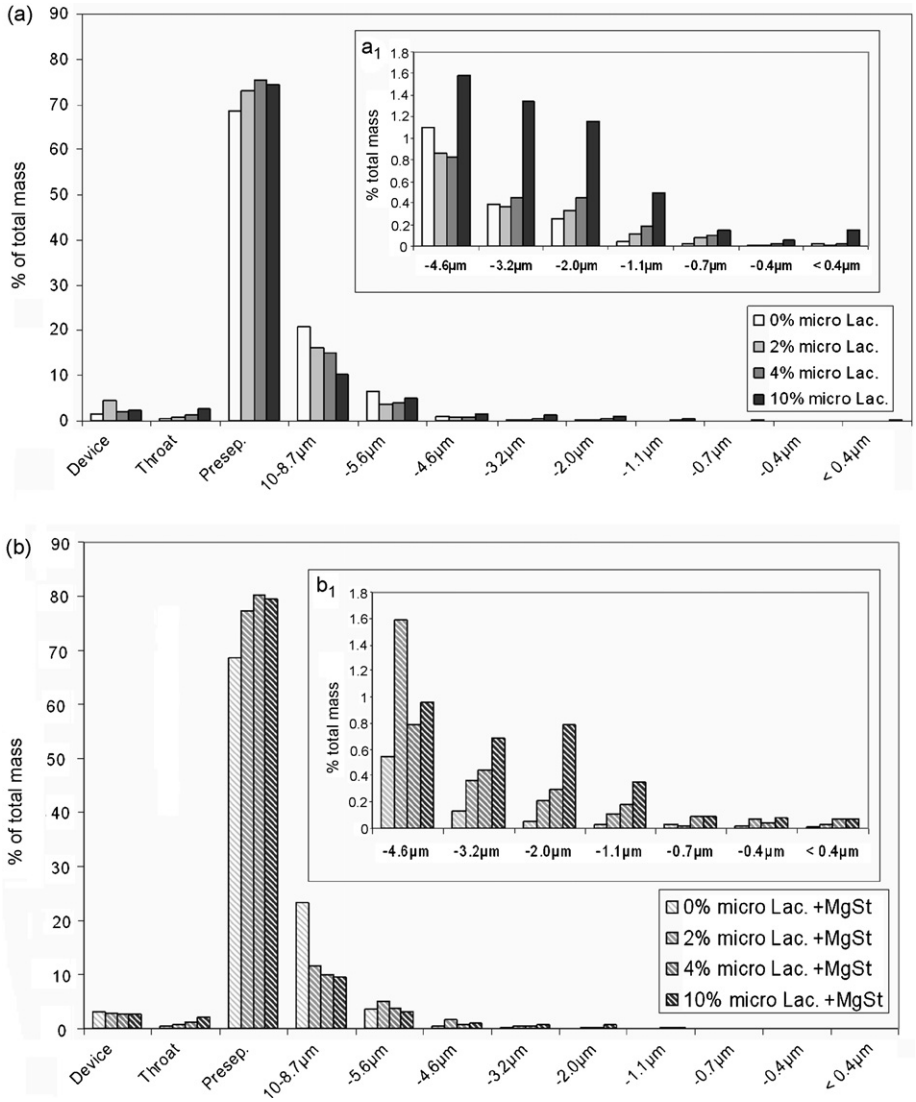

Fig. 5. Aerodynamic particle size distribution of lactose: (a) without MgSt and (b) with MgSt. Details of the range up to 4.6 µm are shown in the inlet (a_1) and (b_1).

the probability of fine lactose reaching the lower stages of the ACI is reduced. The data shown in Fig. 5 also indicate that the amount of lactose retained in the pre-separator for samples with 10% (m/m) of fine lactose is about the same as for samples with 4% (m/m). This points into the direction of a saturation of the active sites with the consequential "extra" amount of fine lactose depositing in the lower stages.

3.2.2. Stability

The change in the aerodynamic behaviour over time was monitored by open storage of the assembled Certihalers containing the various formulations at 20 °C and 30–40% relative humidity for 90 days. Results are shown Fig. 6. The FPF of samples without MgSt decreased by about 8% in absolute terms. The main contributing factor to this behaviour is an increase of lactose–drug interaction, manifested by the increased retention of FF in the pre-separator.

Blends comprising MgSt show, after storage, FPF values similar to the initial results.

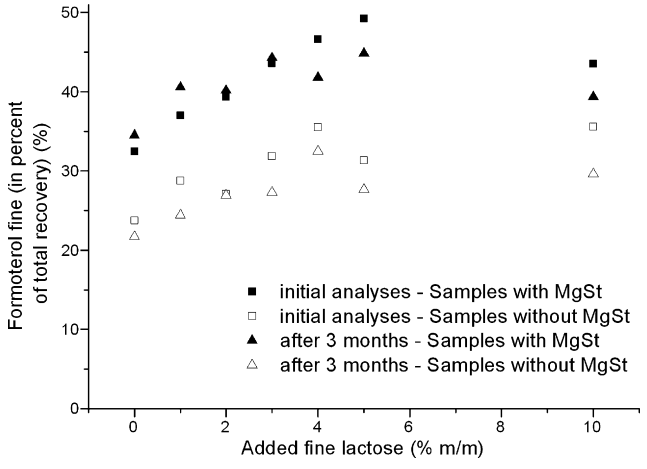

Fig. 6. Formoterol fumarate fine particle fraction of total recovery vs. amount of added lactose.

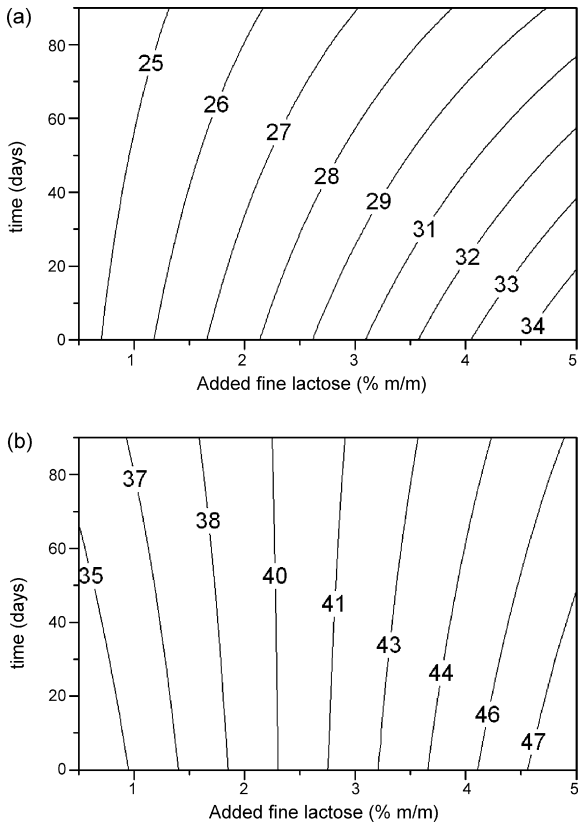

Fig. 7. Contour of the response surface for performance of lactose–formoterol fumarate dry powder inhaler system (a) without MgSt and (b) with MgSt. Lines indicate levels of constant fine particle fraction.

The regression surface (contour plot) for the system was determined (see Eq. (3) and Fig. 7).

$$\mathrm{FPF} = 24.352 + 2.097a + 25.937b - 2.05 \times 10^{-4}c + 0.752ab - 9.38 \times 10^{-3}ac + 7.6 \times 10^{-2}bc, \quad R^2 = 0.93 \tag{3}$$

where a is the added fine lactose (%, m/m), b the concentration of MgSt (%, m/m) and c is the time (days).

Eq. (3) shows that the most influential factor is MgSt, having a positive effect. On the other hand, the negative coefficient for c (time) illustrates the decrease in FPF over time. Fig. 7a confirms that without MgSt there is a strong negative influence of time. In Fig. 7b (blends with MgSt), the profile of the system has changed and a more stable performance over time was observed.

The stability effect described above might be caused by water entering the system. It can act as a plasticizing agent, triggering thermodynamic changes on the surfaces and, possibly, inducing strong particle–particle bonds (Bérard et al., 2002; Price et al., 2002; Young and Price, 2004). Being a substance used to protect against water, MgSt does retain the water and might, at least for a certain period of time, reduce the occurrence of these events (Koivisto et al., 2004). Consequently, the performance remains relatively stable.

4. Conclusions

In order to investigate the influence of fine lactose particles smaller than 10 μm in carrier lactose on the performance of DPI formulations, an adequate particle sizing method has been developed. It was questionable whether this could be achieved by LLD since the particle size range was extremely broad (1–500 μm) and typically more than 90% (v/v) of the particles were coarser than 100 μm. Nevertheless, an LLD method was successfully developed and qualified with respect to sample preparation, parameter settings, dispersing conditions, linearity and sensitivity. As a result, it was found that size and volume fraction of particles smaller than 10 μm being present in coarse carrier lactose can be measured accurately and with appropriate precision up to 10% (m/m).

The developed LLD method was used to investigate the relationship between the amount of fine lactose and performance of a commercial DPI (Foradil Certihaler). An increase in performance of about 3% (absolute) for each percent of added fine lactose was observed. Fine lactose in excess of 5% (m/m) did not show a significant improvement, what probably points to a saturation of the active sites.

APSD of FF particles smaller than 10 μm had a symmetric profile with a maximum at size 2.0–3.2 μm. Fine lactose caused changes only for the absolute values of this distribution. The profile remained the same. On the other hand, the presence of MgSt resulted in a shift of the deposition pattern to an asymmetrical distribution profile. The amount of FF was increased in the size range between 1.1 and 2.0 μm. This might be explained by a potential reduction of drug–drug interactions.

APSD measurements after stability storage indicated that the presence of MgSt was the most relevant factor to stabilise the formulation. The usually observed decrease in FPF during stability is probably associated with moisture, and MgSt protects the formulation against moisture uptake. This benefit of adding MgSt to the formulation is sometimes questioned due to potential risk caused by this agent delivered to the deeper lung. However, evaluations performed in parallel to this study showed that only about 15% (3.5 μg) of the total amount of MgSt present per actuation is delivered to the deeper lung. In toxicological studies it was shown that this amount of MgSt has no negative effect and, therefore, the benefit of using MgSt is greater than the perceived risks.

The APSD data obtained for the carrier lactose and FF in DPI formulations provides further support for the free active sites model as proposed by Young et al. (2005).

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