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Research paper

Dry powder inhalation of antibiotics in cystic fibrosis therapy, part 1: development of a powder formulation with colistin sulfate for a special test inhaler with an air classifier as de-agglomeration principle

A.H. de Boer[a,*], P.P.H. Le Brun[b], H.G. van der Woude[a], P. Hagedoorn[a], H.G.M. Heijerman[c], H.W. Frijlink[a]

[a]*GUIDE: Groningen University Institute for Drug Exploration, Groningen, The Netherlands*
[b]*Central Hospital Pharmacy, Den Haag, The Netherlands*
[c]*Adult Cystic Fibrosis Center, Leyenburg Hospital, Den Haag, The Netherlands*

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Abstract

The aim of this study was to investigate the pulmonary administration of antibiotics as dry powder to patients with cystic fibrosis (CF), as an alternative for nebulization. This part of the study describes the development of a powder formulation with colistin sulfate as model substance. The aim of the new dosage form was to increase pulmonary deposition, therapeutic efficiency and, by that, compliance by the CF patients. A physical powder mixture of colistin and a size fraction of lactose (106–150 μm) was prepared and the mixture was optimized with respect to colistin content (83.3%) for use in a special test inhaler. A laser diffraction apparatus with special inhaler adapter was applied for analysis of the size distribution of the aerosol cloud from the inhaler. The size distributions of the aerosol clouds from the test inhaler at flow rates between 30 and 60 l/min for the optimized formulation showed nearly the same median diameter as that for the primary drug particles. But the X_{100}-value was much lower, because of an effective large particle separation from the inspiratory air by an air classifier in the test inhaler. The results suggest that dry powder inhalation might be a suitable and highly efficient alternative for nebulization of antibiotic drugs in CF therapy.

Keywords: Cystic fibrosis; Inhalation; Test inhaler; Colistin sulfate; Powder formulation; Laser diffraction analysis

1. Introduction

Maintenance treatment with inhaled, nebulized antibiotics is common practice in patients with cystic fibrosis (CF). Two different types of nebulizers are frequently in use: the jet and the ultrasonic nebulizer [1]. The need for a compressor unit or pressurized air for the jet type and electricity for the ultrasonic nebulizer immobilizes the patient to great extent. Regular cleaning and adequate disinfection of the equipment is required in order to prevent contamination with microorgamisms and subsequent colonization of the patient's oropharynx [2,3]. An even greater drawback of nebulizers is their low efficiency. The droplet formation is influenced by many factors and a favourable size distribution for deposition in the target area is not always obtained [4,5]. Output rates are often low and the patient's breathing pattern is a major determinant for the fraction of the dose wasted to the environment [6]. As a result, only 2–12% of the dose for jet nebulizers, and 1–32% of the dose for ultrasonic devices is deposited in the lungs [4,7]. In previous studies with nebulized tobramycin, we found an efficiency of approximately 10% for this drug [8,9].

Dry powder inhalation may provide an alternative for drug nebulization. In a few studies, the use of micronized antibiotics has been reported [10–12]. In these studies, marketed dry powder inhalers (DPI's) with low deposition efficiencies were used and the inhaled doses of dry powder were rather high, resulting in cough in at least one of the studies. A critical aspect of dry powder inhalation for patients with reduced pulmonary function is the inhaler's resistance to air flow. It has been shown that stable adult CF patients of varying severity (between mild, $FEV_1 = 72\%$, and severe, $FEV_1 = 36\%$) can attain the same flow rates as normals through air flow resistances corresponding with that for the Glaxo Rotahaler®, or higher [13]. In this

* Corresponding author. GUIDE: Groningen University Institute for Drug Exploration, Department of Pharmaceutical Technology and Biopharmacy, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. Tel.: +31-50-363-3286; fax: +31-50-363-2500.

E-mail address: a.h.de.boer@farm.rug.nl (A.H. de Boer).

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study, only for air flow resistances $<0.015\ kPa^{0.5}.\ min.\ l^{-1}$, a significant difference was found between CF patients and normals (or COPD patients), but these resistances are beyond the range of that for marketed DPI's. This suggests that adult CF patients can use the same types of inhalers as asthmatics and mild COPD patients. Only for very young asthmatic children between the ages of 3 and 6 years, it has been reported that they may not all have the optimal inhalation technique to operate a DPI with moderately high air flow resistance [14]. It has also been shown that children with CF generate nearly the same PIFR as asthmatics during lung function testing [15]. The difference in this study was only 5%, although good comparison is not possible, because the difference in mean age between the group of asthmatics (8.9 years) and CF patients (16.6 years) was nearly by a factor 2. In conclusion, it is recommended that a DPI for children with CF has a moderate to low air flow resistance and is effective at flow rates between 30 and 60 l/min.

A powder formulation for inhalation has to meet criteria for dose reproducibility, physico-chemical stability and fine particle deposition in the respiratory tract. The aerodynamic particle size distribution of the drug has to be between approximately 0.5 and 7.5 μm. Within this range, many different subranges for the median aerodynamic diameter have been presented as the most favourable (e.g. refs [4,16–18]), dependent on the target area and the inspiratory flow rate.

Micronized powders exhibit poor flowability and extreme agglomeration and adhesion tendency. They have to be processed into a suitable, preferably free flowing formulation for accurate dose reproducibility, especially in the low dose-range, used for inhalation. Lactose (or glucose) is often added to the drug, either as a diluent (e.g. for preparing spherical pellets) or as a carrier (for preparing adhesive mixtures). Different types of lactose as well as many different size distributions or mixtures of different size fractions have been proposed (e.g. refs [19–21]). It has been recognized that carrier surface properties are very relevant to the drug-to-carrier interaction (e.g. refs [22–25]). On the other hand, the use of lactose excipient in inhalation powders has been criticized because of irritation during inhalation [26], cough and bronchoconstriction [16] as well as local side effects from deposition of drug bound-to-carrier in the throat [27].

Most marketed DPI's measure doses between 5 and 25 mg (including the excipient). Maintenance therapy for CF patients with colistin sulfomethate in many countries includes nebulization of 80 mg (for children) and 160 mg (for adults) twice a day. Because sulfomethate is hydrolized in vivo to colistin sulfate, and the free drug has a much higher bactericidal activity than the sulfomethate (e.g. in terms of minimal bactericidal concentration), colistin sulfate seems to be a suitable alternative for dry powder inhalation. If lung deposition upon nebulization is only for 10% of the dose, it can be calculated that 8–16 mg of the sulfomethate shows already antibacterial action. For an equivalent effect from an efficient DPI with 30–40% lung deposition, the total dose could be reduced to 25–40 mg (excluding excipient) or even less, considering the higher activity and absence of a lag time for hydrolysis.

This paper describes the development of a dry powder formulation for colistin sulfate (physical mixture of the drug with a narrow lactose sieve fraction) and the testing of this formulation in vitro with a highly efficient air classifier based test inhaler, having a moderate air flow resistance. The objectives of the study were:

- to obtain highest possible fine particle fraction;
- to reduce possible adverse effects like cough, as reported previously, by minimizing the amount of powder being inhaled (minimal lactose content in the formulation and separation of larger lactose particles from the inspiratory air); and
- to develop a system that can also be applied for pulmonary administration of other types of antibiotics.

2. Materials and methods

2.1. Starting materials

Colistin sulfate was obtained from Duchefa Farma (Haarlem, The Netherlands). The powder was micronized by fluid energy milling (GfM, Hamburg, Germany) and used as such for preformulation experiments. Because the size distribution produced by the jet mill was not satisfactory for inhalation experiments, further size reduction of a small sample (50 g) was obtained by 26.5 h of ball milling (on a home constructed drive). A ceramic container of 750 ml, filled with china balls of different sizes to a filling degree of 67% was used. Only the ball milled product has been used for the in vitro inhalation experiments.

Small batches (50 g) of lactose size fractions 63–105 and 106–150 μm were derived from Pharmatose 100M (DMV International, Veghel, The Netherlands) by 20 min vibratory sieving (in a Fritsch Analysette 3, Idar Oberstein, Germany) and subsequently 10 min air jet sieving (in an Alpine A200 LS, Augsburg, Germany).

2.2. Characterization of the starting materials

Particle size distributions of the starting materials were measured with a Sympatec HELOS Compact model KA laser diffraction apparatus (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a 100 mm lens and the Fraunhofer theory. The samples were dispersed in the laser beam with a RODOS dry powder disperser at 4 bar.

Adhesiveness (tendency to form adhesive mixtures) and cohesiveness (tendency to form pellets) of the micronized colistin powder were examined with appropriate mixing and pelletization techniques, such as tumbling mixing with pelletizing grains and screening through a sieve. Different moisture contents of the active ingredient in the preformu-

lation phase were obtained after conditioning in a climate cabinet at different relative humidities (Heraeus, VTRK150, Heraeus Instruments GmbH, Hanau, Germany). The actual moisture contents of colistin samples after conditioning were determined with an infrared drying balance (Sartorius MA40, Sartorius AG, Göttingen, Germany).

The particle density of the antibiotic drug was measured with a Helium pycnometer (Multi Pycnometer, Quanta-Chrome Corp. Syosset, USA).

2.3. Preparation of physical powder mixtures for inhalation experiments

Several experiments were undertaken in the preformulation phase to obtain spherical pellets or adhesive mixtures with the micronized colistin sulfate. For these experiments, the concentration (in the mixture) and the moisture content of the antibiotic drug were varied, as well as the size fraction of the lactose excipient and two different size fractions of colistin were investigated. However, scanning electron and light microscopic photographs of the mixtures revealed that neither pellets nor adhesive mixtures could be obtained with mixing techniques, that were used successfully in the past for anti-asthmatic drugs. Therefore, it was decided to use physical mixtures of lactose and colistin sulfate ($X_{50} = 2.14 \pm 0.07$ μm) with the drug having a moisture content of 7.3%. Mixtures in batch sizes of 25 g were prepared in a tumbling mixer (Turbula T2C, W.A. Bachofen, Basel, Switzerland) at 90 r.p.m. Mixing times were 10 min in a stainless steel mixing container in order to minimize tribocharge. Different weight percentages of colistin (25, 50, 75 and 83.3%, respectively) were applied in the formulation.

2.4. Dry powder inhalers

For the in vitro deposition experiments with the prepared mixtures, a test inhaler as depicted in Fig. 1 was used. This test inhaler is a derivative of the inhaler concept with air classifier described previously [28–30]. The test inhaler consists of machined polycarbonate parts and has an air classifier that enables near-complete retainment of larger particles. Manually weighed doses are inserted in the dose compartments of the disk before disk and cover plates are joined together. Transport of the compartment disk after assembling of all inhaler parts is by rotation of the top cylinder. During inhalation, the air flow conveys the dose from the compartment disk to the air classifier chamber where particles larger than the cut-off diameter circulate by action of the centrifugal force during the whole inhalation manoeuvre. During circulation, shear and impact forces occur. They cause either disintegration of drug agglomerates (e.g. pellets) into much smaller (preferably primary) entities, or detachment of drug particles from carrier crystals in adhesive mixtures. Only particles smaller than the cut-off diameter are discharged by the drag force which, for the test inhaler used in this study, is <30 μm at 30 l/min, respectively, <15 μm at 60 l/min for crystalline alpha lactose monohydrate particles (wedge shaped crystals with a true density of 1.54 g/cm^3). One of the functions of the lactose crystals in the physical mixtures with colistin is to keep the inner walls of the air classifier chamber free from adhering micronized colistin particles (sweeper action).

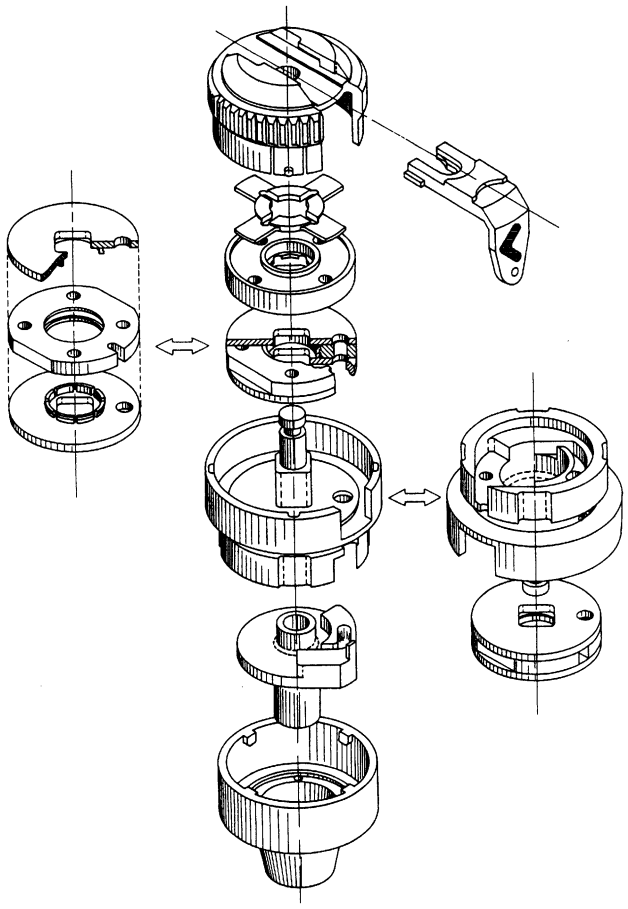

Fig. 1. Test inhaler for the colistin dry powder formulation.

A marketed capsule inhaler (Cyclohaler®, Pharmachemie, Haarlem, The Netherlands) was used as reference inhaler (Fig. 2). This type of inhaler is also known as the Aerolizer® or the ISF® inhaler and has been described previously, e.g. by Nielsen et al. [31]. Transparent capsules (no. 3) were filled with 10 mg of drug and the capsules were sealed before use to prevent sliding of the cap over the body during perforation.

2.5. Laser diffraction analysis (LDA) of the aerosol cloud

The particle size distribution of the aerosol cloud from the inhalers was measured with a Sympatec HELOS Compact model KA laser diffraction apparatus (Sympatec GmbH, Clausthal-Zellerfeld, Germany: 100 mm lens). A special inhaler adapter was used (GUIDE prototype, Groningen, The Netherlands) for precise control of the inspiratory flow rate through the inhalers [32]. The laser diffraction

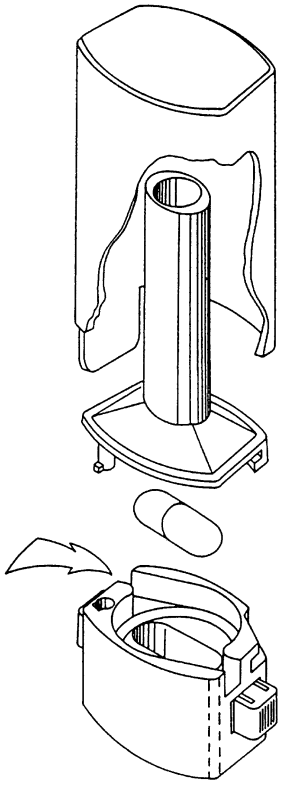

Fig. 2. Pharmachemie Cyclohaler®.

measurement was triggered (start and stop of the measurement) on the optical signal on one of the detector channels for fine particles. Inhalation time was 3 s. The Fraunhofer theory was used for calculating size distributions from the laser diffraction patterns, because this theory gives more realistic values for dry particles dispersed in air. This has different reasons, as has been discussed previously [5].

2.6. Cascade impactor analysis (CIA) of the aerosol cloud

For cascade impactor analysis, a four stage glass constructed cascade impactor of the Fisons type (Elgebe, Leek, The Netherlands) was used with a dry bent induction port. The stages were filled with 20 ml of pure water as solvent. The impactor has a theoretical cut-off diameter for the second stage of 9.2 μm at 60 l/min for colistin sulfate particles with a true density of $\rho_0 = 1.36$ g/cm^3. The amount of colistin sulfate retained from the different impactor stages was analyzed with a modified Lowry method [33].

2.7. Inhalation experiments

Inhalation experiments were started with a physical mixture containing 25% (by weight) of colistin sulfate and 75% of the lactose fraction 63–106 μm. The air classifier based test inhaler was used for two inhalation series of six doses of 20 mg each at 30 and 60 l/min, respectively. With a colistin sulfate dose of only 5 mg per inhalation (25% of 20 mg), five to eight inhalations would be necessary to administer a total dose of 25–40 mg. In order to minimize the number of inhalations, the colistin concentration in the powder was increased to 50, 75 or 100%. All formulations were inhaled with the same test inhaler at 60 l/min (six doses of 20 mg per mixture).

Because some minor pollution of the air classifier was found for the 100% colistin compound (in the absence of sweeper action), it was decided to continue with a mixture containing 16.7% lactose. In this mixture the lactose was substituted by a somewhat coarser size fraction (106–150 μm), because larger crystals are more efficient in keeping the classifier walls clean. For each experiment, six doses of 12 mg each (containing 10 mg colistin sulfate) were inhaled with the test inhaler, and the size distributions of the aerosol clouds were measured with LDA (at 20, 30, 40, 50 and 60 l/min) as well as with CIA (only at 60 l/min).

For the Cyclohaler®, only the 100% colistin compound was tested, because the lactose excipient has no function for this type of inhaler (not for powder disintegration, nor for capsule emptying, nor for sweeper action). On the contrary, the large crystals were found to block the discharge holes in the capsule ends and to disturb drug release. From the Cyclohaler®, six doses of 10 mg each were inhaled for each measurement.

3. Results

The size distributions obtained from laser diffraction analysis of colistin sulfate before and after comminution in the ball mill are presented in Fig. 3. The volume median diameter (X_{50}-value ± standard deviation) decreased from 6.43 (±0.03) to 2.14 (±0.07) μm after 26.5 h of milling, whereas the X_{100}-value increased slightly due to some aggregation. Laser diffraction analysis of the lactose samples showed that the prepared fractions contained no particles in the size range 10–63 μm after air jet sieving.

Table 1 summarizes the mean X_{50}-values (with standard deviations) from laser diffraction measurement of the aero-

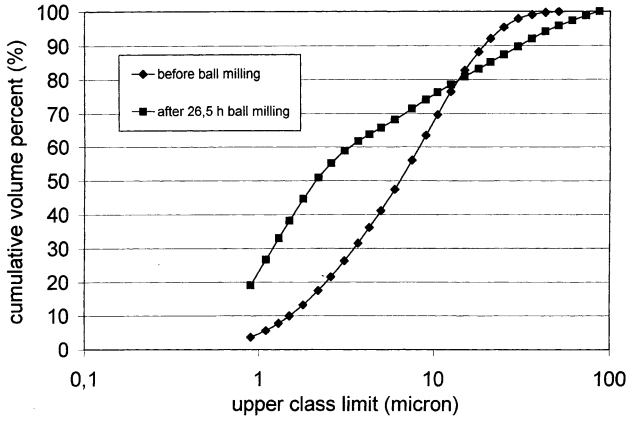

Fig. 3. Micronized colistin sulfate before and after (26.5 h) further size reduction in the ball mill: mean results from dry laser diffraction measurement with RODOS dispersion at 4 bar ($n = 3$).

Table 1
Dose weight per inhalation, number of inhalations per experiment and X_{50}-values (with standard deviations) of the aerosol clouds for various formulations inhaled with the test inhaler and Cyclohaler® at 30 and 60 l/min[a]

Mixture (% colistin)	Lactose fraction (μm)	Dose weight per inhalation (mg)	Number of inhalations (−)	Mean X_{50}-value from LDA (standard deviation)	
				30 l/min	60 l/min
TI 25	63–106	20	6	2.49 (0.28)	2.15 (0.10)
TI 50	63–106	20	6	–	2.03 (0.14)
TI 75	63–106	20	6	–	2.07 (0.07)
TI 83.3	106–150	12	6	2.36 (0.29)	2.24 (0.08)
TI 100	–	20	6	–	2.24 (0.21)
CH 100	–	10	6	–	24.3 (7.0)

[a] TI: test inhaler; and CH: Cyclohaler®.

sol clouds from the test inhaler at 30 and 60 l/min. The table also shows the dose weight per inhalation and the total number of inhalations for these experiments. The whole cumulative size distribution curves for the aerosol clouds from the test inhaler (at 30 and 60 l/min) for the mixture with 25% colistin sulfate are given in Fig. 4. From content uniformity testing (15 samples of 20 mg), an actual colistin sulfate content in this mixture of 24.8% was found (coefficient of variation = 2.8%). For the inhalation experiments with this mixture, also a mass balance was calculated from the weighed doses and retained masses from the air classifier. Table 2 presents the average values (with standard deviations) for the weighed and delivered dose ($n = 6$) at 30 and 60 l/min. For the experiments at 60 l/min, the average delivered colistin dose (5.48 mg) was slightly higher than the nominal dose (4.96 mg), which most likely is the result of the discharge of a few lactose crystals.

The mean size distributions from LDA of the aerosol clouds from the test inhaler at 60 l/min for the mixtures with 25, 50 and 75% colistin sulfate are given in Fig. 5. For all mixtures, the same lactose fraction of 63–106 μm was used. Fig. 5 also shows the size distributions from the experiments at the same flow rate with 100% active substance, using both the test inhaler and the marketed Cyclohaler®. The effect of flow rate on the size distribution of the drug particles in the aerosol cloud for the mixture with 83.3% colistin sulfate from the test inhaler is shown in Fig. 6.

The results given in Fig. 7 are from the experiments with the cascade impactor for the mixture with 83.3% colistin sulfate using the test inhaler. The majority of the fraction derived from the 3rd and 4th stage (particles smaller than 9.2 μm) is likely to enter the lungs. The fractions on stages 1 and 2 represent the larger drug particles that are deposited in the throat. The fractions given in Fig. 7 are for pure colistin sulfate only; the lactose particles were retained in the test inhaler.

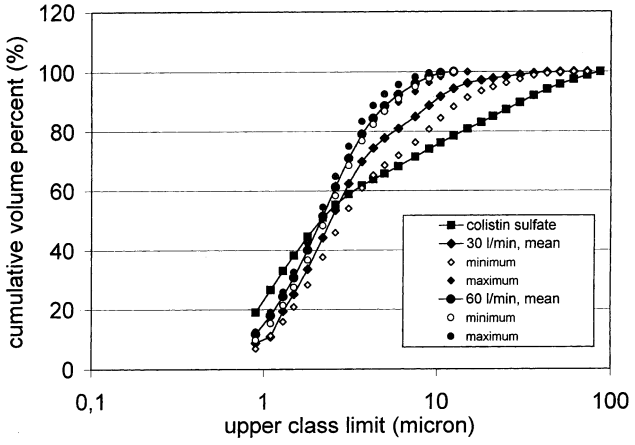

Fig. 4. Results from laser diffraction analysis of the aerosol cloud from the test inhaler at 30 and 60 l/min for the formulation with 25% colistin sulfate and lactose size fraction 63–106 μm (six subsequent doses of 20 mg). Mean, maximal and minimum values in comparison with the (mean) size distribution of the pure colistine sulfate (26.5 h ball mill) from RODOS dispersion.

4. Discussion

The size distribution of the used colistin in Fig. 3, shows that even after ball milling 30–40% of the primary particles is unlikely to enter the target area. This should be taken into account when interpreting the laser diffraction and cascade impactor data. Ball milling does not yield the most favourable size distribution for inhalation, but applying this technique was inevitable considering the small sample being available. One of the consequences of applying this comminution principle is a certain extent of aggregation into hard

Table 2
Weighed (lactose and drug) and delivered (drug) dose for the mixture with 25% colistin sulfate from the test inhaler at 30 and 60 l/min[a]

	30 l/min	60 l/min
Nominal drug dose (mg)	4.96	4.96
Weighed dose (mg)	19.88 (0.97)	20.79 (0.44)
Retained carrier (mg)	15.66 (1.14)	15.32 (0.60)
Delivered drug dose (mg)	4.22 (0.58)	5.48 (0.68)
Delivered drug dose (%)	21.3 (3.19)	26.3 (2.91)

[a] The difference is the result of the efficient large particle retainment by the air classifier. Values between brackets are standard deviations, $n = 6$.

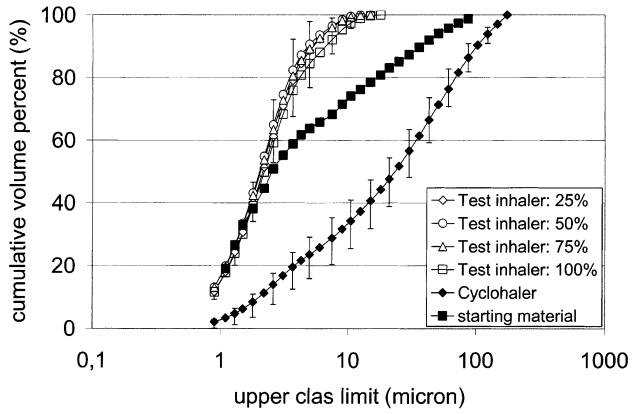

Fig. 5. Results from laser diffraction analysis of the aerosol cloud from the test inhaler at 60 l/min for four different formulations with 25, 50, 75 and 100% colistin sulfate, respectively (six subsequent doses of 20 mg for each formulation) and lactose size fraction 63–106 μm. Mean values in comparison with the size distribution of the pure colistin sulfate (26.5 h ball mill) from RODOS dispersion and that for the aerosol cloud (mean of 6 × 10 mg) from the Cyclohaler® at 60 l/min.

particle clusters that can not be disintegrated during inhalation. The use of an air classifier enables retainment of such large aggregates, and lactose excipient particles however. This answers the goal to minimize the amount of powder being deposited in the throat and upper part of the lungs. The use of a physical powder mixture (instead of an adhesive mixture) fulfils the desire to become widely independent of the type and size distribution of the excipient used in the formulation. It also makes the formulation less colistin specific (no drug-to-carrier interaction).

The used air classifier proved to be very effective with respect to the powder de-agglomeration and withdrawal of larger particles (of both colistin and lactose). Fig. 4 and Table 1 show that the mean X_{50}-values of the aerosol clouds

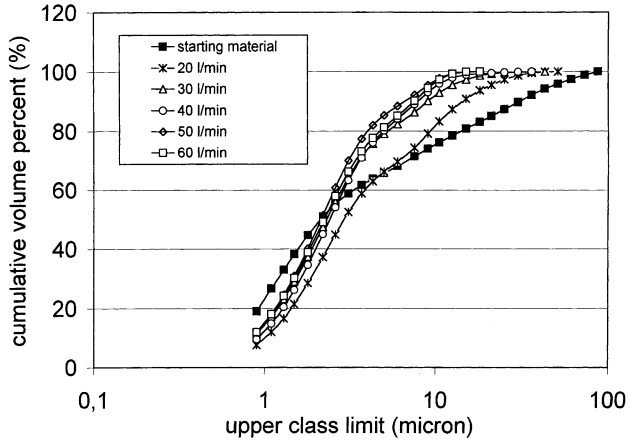

Fig. 6. Results from laser diffraction analysis of the aerosol cloud from the test inhaler at different flow rates (20, 30, 40, 50 and 60 l/min) for a formulation with 83.3% colistin sulfate and lactose size fraction 106–150 μm (six subsequent doses of 12 mg for each flow rate). Mean values in comparison with the (mean) size distribution of the pure colistin sulfate (26.5 h ball mill) from RODOS dispersion.

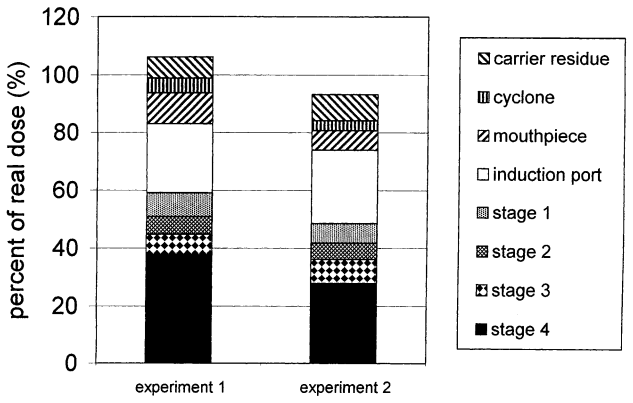

Fig. 7. Cascade impactor results for the mixture with 83.3% colistin sulfate (and lactose size fraction 106–150 μm) from the test inhaler at 60 l/min ($n = 2 \times 10$ doses of 12 mg).

from this inhaler at 30 and 60 l/min are similar to the X_{50}-value of the starting material from RODOS dispersion (2.14 ± 0.07 μm). Fig. 4 also shows the effective large particle withdrawal by the air classifier: the mean X_{100}-values are only 40 and 12 μm at 30, respectively, 60 l/min (in spite of the presence of 75% lactose having a size fraction of 63–106 μm).

The effect of the colistin concentration in the formulation appears to be not very critical for the test inhaler used. In Fig. 5, the X_{50}-values for the clouds from the formulations with 25, 50, 75 and 100% colistin sulfate at 60 l/min are nearly the same. Moreover, the whole size distribution curves are comparable, including the X_{100}-values, which are all smaller than 17.5 μm. In contrast, the difference between the test inhaler and the marketed Cyclohaler® for the 100% compound in this figure is remarkable. The median particle diameter of the aerosol cloud (at 60 l/min) from the test inhaler is much smaller compared to that from the Cyclohaler® (Table 1). The upper size limit of the aerosol cloud from the capsule inhaler (175 μm), in the absence of lactose, is even higher than that for the drug from RODOS dispersion (87 μm). The difference confirms the high disintegration efficiency of the air classifier and it may be concluded that the capsule inhaler is not suitable for the developed colistin formulation.

The effect of inspiratory flow rate on the size distribution of the aerosol cloud for the final formulation with 83.3% colistin sulfate from the test inhaler is negligible between 30 and 60 l/min (Fig. 6). The X_{50}-values are again nearly the same (ranging from 2.15 ± 0.05 to 2.43 ± 0.16 μm); only the X_{100}-value decreases slightly with increasing flow rate from 28 μm at 30 l/min to 17 μm at 60 l/min. This is a consequence of the flow dependent cut-off diameter of the air classifier. Only at 20 l/min, the X_{50}-value is somewhat higher: 3.10 ± 0.68 μm.

From Fig. 6, a volume percent of 95% smaller than 9 μm can be derived for the test inhaler operated at 60 l/min. This seems not in agreement with the cascade impactor result in Fig. 7, showing that only 40.3% of the dose has been depos-

ited on the stages 3 and 4 at the same flow rate. This comparison can not be made without making several corrections however. The fine particle fraction (with aerodynamic diameter <9.2 μm) obtained from cascade impactor analysis is expressed as percent of the weighed dose. The size distribution of the aerosol cloud from laser diffraction is for the emitted dose, which is considerably lower than the weighed drug dose as a consequence of large particle retainment and losses in the (induction port to the) cascade impactor. A simple calculation may explain this difference. With a cut-off value of approximately 15 μm for the air classifier at 60 l/min, only 80% of the weighed dose is emitted from the inhaler's mouthpiece for the starting material presented in Fig. 3. Also as percent of the weighed dose, only approx. 70% of the particles is within the geometric size range <7.9 μm (as measured with LDA), which equals an aerodynamic diameter of 9.2 μm (the theoretical cut-off diameter of the second impactor stage for particles with a density of 1.36 g/cm^3). However, nearly 22% of the dose has been deposited in the induction port to the cascade impactor, whereas the total recovery was only 94%. It is known from previous investigations that the losses reported here above are particularly for the fines. So, after correction for these fines, only approximately 70 minus $(22 + 6)$ equals 42% of the weighed dose may be expected on the 3rd and 4th impactor stages. This is in fairly good agreement with the 40.3% actually found, especially considering also the losses in connecting tubes and the poor cut-off efficiencies of the various impactor stages at 60 l/min (at which flow rate the Reynolds numbers in all nozzles exceed the values for laminar flow). The fact that mass fractions (from CIA) are compared with volume fractions (from LDA) is less relevant, because there are no reasons to assume that particle density is different for different size fractions. So, the volume distribution equals the mass distribution.

5. Conclusions

With an approximate mass fraction of 40% of the dose emitted as fine particles, it may be expected that a total inhaled dose of 20–40 mg of colistin sulfate is sufficient to obtain a total lung deposition of 8–16 mg. In a formulation with only 16.7% of lactose, total dose weight administered would have to be between 24 and 48 mg, which can be easily be divided into two to four inhalations. An even lower dose as sulfate might yield a similar effect as the nebulization of 80–160 mg of aqueous sulfomethate solution considering the reported higher bactericidal activity for the sulfate. The fine particle dose may be further increased when a more favourable size distribution of the antibiotic drug is used: the X_{100}-value should preferably be smaller than 10 μm. Using the air classifier based disintegration principle, powder deposition in the patient can be confined to the active ingredient only, whereas the advantages (such as a sweeper effect) of the use of an excipient are still available. This is less burdensome for the patient and will reduce the adverse side effects like cough. Taking also the ease of administration into account, it is expected that dry powder inhalation of antibiotic drugs may become a good alternative for nebulization. For this reason, it was decided to start a patient study with the dry powder formulation test system. The results of this study are reported and discussed in part 2 of this series.

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