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## Optimisation of dry powder inhalation

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## Chapter 11

### **Design and in vitro performance of a disposable inhaler (Twincer<sup>®</sup>) with multiple air classifier technology for high powder doses**

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**Abstract**

Dry powder inhalation of antibiotics in cystic fibrosis (CF) therapy may be a valuable alternative for wet nebulisation, because it saves time and it improves lung deposition. In this study, it is shown that the use of multiple air classifier technology enables effective powder dispersion of large amounts of micronised powder (up to 25 mg).  $X_{50}$ -values from laser diffraction analysis of a colistin aerosol obtained with the Twincer<sup>®</sup> disposable inhaler (containing multiple air classifier technology) are practically the same as those for the pure drug in the range of dose weights between 0 and 25 mg. Only for the highest dose weights, a minor fraction (5 to 7.5%) of small agglomerates (5 to 15  $\mu\text{m}$ ) is released from the inhaler. Moreover, the size distribution of the aerosol is practically the same at 1 and 4 kPa too. Cascade impactor results confirm the good inhaler performance. Unprocessed micronised particles or soft spherical agglomerates can be used, and special particle engineering processes are not necessary. Only a minor fraction of coarse sweeper crystals in the formulation is desired to reduce the inhaler losses to less than 7.5% at 4 kPa. The classifiers can be designed to retain these crystals with more than 95% efficiency.

*Keywords:* Antibiotics, Cystic fibrosis (CF), Dry powder inhaler, Multiple air classifier technology, Sweeper crystals, Twincer<sup>®</sup>

## 1. Introduction

In the past decade, a great interest has been developed in pulmonary administration of high doses, e.g. for systemically active substances that can not be given via the oral route because of a poor bioavailability. Such drugs have to be delivered to the peripheral airways where the permeability is high and the surface area for absorption is large (Patton 1996; Kim and Folinsbee 1997; Groneberg et al., 2003). The preferable drug particle size for deposition in the small airways is between 2 and 4  $\mu\text{m}$  under the conditions of quiet breathing and a certain period of breath hold (Gerrity, 1990; Martonen and Katz, 1993; Schulz, 1998). Most systemically active drugs via the pulmonary route are peptides and proteins which have to be stabilised with sugar glass technology, using spray drying or spray-freeze drying techniques (Gribbon et al., 1996; van Drooge et al., 2004). Sugar glass technology increases the amount of powder to be dispersed, and the powders are frequently highly hygroscopic and cohesive. All these factors contribute to the low (and highly variable) bioavailabilities reported for drugs like insulin so far. They result in substantial drug losses in the device (including the dose system) and upper airway deposition of insufficiently dispersed powders, or particles released with too high velocity (Newhouse et al., 2003; Patton et al., 2004).

A special group of high dose drugs administered via the pulmonary route are antibiotics, for instance in cystic fibrosis (CF) therapy. CF is a hereditary disease, characterised by secretions of extremely high viscosity from exocrine glands in the airways (Smith et al., 1996). The increased viscosity of the mucus hinders clearance of micro-organisms from the respiratory tract (Geddes, 1997). The inflammatory response to infected sites mainly with *Haemophilus influenzae* and *Staphylococcus aureus* during childhood, followed by *Pseudomonas aeruginosa* in later years (Touw et al., 1995; Wood, 1996) gradually causes airway damage, which is irreversible and eventually leads to death (Ferrari et al., 2002). Different target areas for antibiotic drugs in CF have been mentioned, including the bronchial lumen (e.g. Ramsey 1996; Van Devanter and Montgomery, 1998), the smaller bronchioles (Touw et al., 1995; Geddes, 1997) and more recently the peripheral airways (Tiddens, 2002). Different antibiotics are used for inhalation by nebulisation, such as gentamicin (Newman et al., 1985), colistin sulfomethate (Turnidge et al., 2001) and tobramycin (Le Brun et al. 1999). As a consequence of the high doses (e.g. 160 mg for gentamicin and colistin and 300 mg for tobramycin respectively) to be given, conventional nebulisation may require up to 30 min. This influences the quality of life and is disadvantageous from the viewpoint of patient compliance. An alternative for wet nebulisation is dry powder inhalation. Dry powder inhalers for gentamicin (Goldman et al., 1990; Crowther Labiris et al., 1999), colistin sulphate (Le Brun et al., 2002), colistin sulfomethate (Flynn et al., 2000) and tobramycin sulfate (Newhouse et al., 2003) have been presented, with varying success. These studies have shown that comparable sputum (or plasma) concentrations and lung depositions can be obtained as from nebulisation of the same drugs, but the doses inhaled were rather high for dry powder inhalers. They varied from 160 - 180 mg for gentamicin, 150 mg for tobramycin sulfate (PulmoSphere formulation), 30 - 150 mg for colistin sulfomethate to 25 mg for colistin sulfate. The reasons for these high doses are ineffective powder dispersion which leads to poor lung deposition. The dose weights mentioned are for the pure drug, except for a (tobramycin) PulmoSphere formulation (Newhouse et al., 2003) which contained 10% excipient. As a result, inhalation of a relatively large number of powder quantities for a single dose are necessary, varying from 3 (for colistin sulfate) to 32 (for gentamicin) actuations.

The aim of this study was to design and develop a 'passive (breath controlled) dry powder inhaler' with which high doses of antibiotics or therapeutic protein (or lipophilic drug) containing sugar glass formulations can be administered effectively to the deep lung in one or two inhalation manoeuvres. Being designed as a disposable device, the inhaler is also

meant for pulmonary delivery of other drugs, for example medication that has to be given only one (e.g. vaccines). The inhaler has been designed to produce a high fine particle fraction at a relatively low inspiratory effort without using particle-engineered technologies. This will make it possible to inhale slowly. It also minimises the excipient concentration in the inhalation powder, which (in combination with excipient retention by the inhaler) reduces the amount of powder to be inhaled. In this paper we describe the development of multiple classifier technology for this purpose.

## 2. Materials and methods

### 2.1. The disposable Twincer<sup>®</sup>, multiple classifier dry powder inhaler

The basic design of the disposable multi classifier dry powder inhaler (Twincer<sup>®</sup>) is shown in Fig. 11.1.

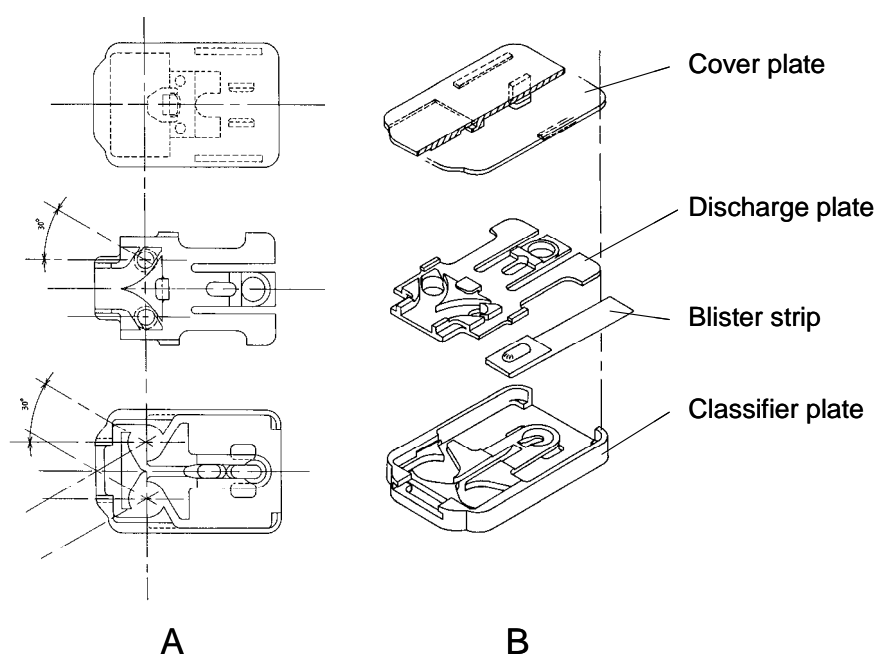


Figure 11.1. Presentation of the Twincer<sup>®</sup> as a disposable inhaler for high doses of moisture sensitive materials stored in a blister. The drawing shows the basic concept which consists of three plate-like inhaler parts and the blister with a long pull-off strip.

Basically, the inhaler consists of three plate-like parts and a blister for the powder formulation with the drug. The plate-like parts have various projections and depressions which comprise the air flow passages and the blister chamber when the parts are assembled. The blister has a long cover foil which is folded and sticks out from the rear end of the inhaler. By pulling the cover foil, the blister is opened and connected to the powder channel. Air passing through the powder channel during inhalation entrains the powder from the blister, and the powder flow is divided between two (or more) parallel classifiers in the bottom plate (classifier plate) of the inhaler. The classifiers shown in Fig. 11.1 have three air supply channels each, but there may be different numbers. Instead of having basically a cylindrical wall, the classifier may also be polygonal, depending on the type of powder formulation to be processed (de Boer et al., 2005a). For the Twincer<sup>®</sup> depicted in Figs. 11.1 and 11.2, the discharge channels are circular holes (in the discharge plate) with a rim

projecting into the classifier chamber. The ratio of the diameter of the discharge hole to that of the classifier chamber (and the height of the rim around the discharge hole) can be varied to control the residence time for the powder in the classifier and the efficiency with which carrier or sweeper particles are retained. The discharge channels end in two grooves in an elevated part of the discharge plate. These grooves are united in what becomes the mouthpiece channel of the inhaler when the cover plate is put in place. Bypass channels around the discharge holes are used to reduce the inhaler accumulations and to control the total inhaler resistance.

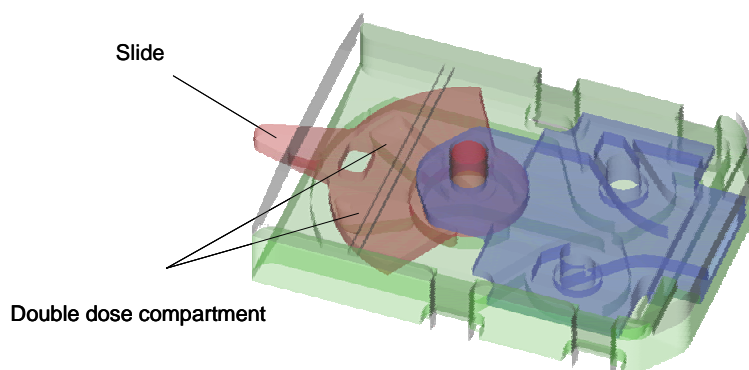


Figure 11.2. Presentation of the (machined) concept used for a proof of principle with (2 x 12.5 mg) colistin sulfomethate in 7 healthy volunteers and 10 CF patients (results presented in part 2). The concept has no blister, but two storage compartments for the drug dose that can be connected with the air supply and powder channel by means of a slide.

The example shown in Fig. 11.1 is the basic design of the Twincer<sup>®</sup>. Various concepts with different classifier designs for different applications have been constructed and tested. Fig. 11.2 shows the concept used for a proof of principle with colistin sulfomethate in CF patients and healthy volunteers (publication in preparation). This concept has no blister, but two different dose compartments (filled manually) which can be connected with the powder channel by means of a slide. For this study, the drug dose has been inhaled in two equal parts of 12.5 mg, instead of 25 mg at once, in order to minimise the burden for the patient. More details (and variations) of the Twincer<sup>®</sup> concept and its working principle are given by de Boer et al. (2004).

## 2.2. Materials

Micronised colistin sulfomethate was purchased from Alpharma (Copenhagen, Denmark). The size distribution of the sample obtained from laser diffraction analysis (RODOS dispersion at 3 bar) was:  $X_{10} = 1.03 \mu\text{m}$ ;  $X_{50} = 5.08 \mu\text{m}$  and  $X_{90} = 10.41 \mu\text{m}$ . Pharmatose 110M and 80M (starting materials for the preparation of special size fractions of sweeper crystals) were supplied by DMV International (Veghel, The Netherlands). A Pulmicort<sup>®</sup> 200 Turbuhaler<sup>®</sup> (reference device) was obtained from the local pharmacist. All Twincers<sup>®</sup> used in this study were machined devices, constructed by the research workshop of the Faculty of Medicine (University of Groningen).

### 2.3. Methods

For micronisation of the colistine sulfomethate to the desired size distribution for inhalation, a spiral jet mill with 0.8 mm nozzle (50 AS, Alpine, Augsburg, Germany) was used (air pressure: 2 x 6 bar). Lactose size fractions (sweeper crystals) of 63-100  $\mu\text{m}$ ; 150-200  $\mu\text{m}$  and 250-355  $\mu\text{m}$  were derived from Pharmatose 110M and 80M respectively, by 20 min vibratory sieving (Analysette 3, Fritsch, Idar-Oberstein, Germany) followed by 20 min air jet sieving (A200, Alpine). Sweeper crystals and colistine sulfomethate were either mixed (10 min) in the indicated quantities (see text), using a tumbling mixer with a (160 ml) stainless steel mixing container (Turbula 2TC, WA Bachofen AG, Basel, Switzerland), or weighed separately into the dose compartment of the Twincer<sup>®</sup>.

Size distributions of the starting materials (drugs and sweeper fractions) during the concept development phase were measured with laser diffraction technique, using a HELOS BF MAGIC (Sympatec, Clausthal-Zellerfeld, Germany) with standard Windox software. Powders were dispersed with a RODOS dry powder disperser (Sympatec) at 0.5; 3 or 5 bar (see text). Computations of diffraction data (obtained with a 100 mm lens for the drug) into size distributions were made with the Fraunhofer theory. For the sweeper fractions 200 and 500 mm lenses were used. The size distributions of the aerosols from the Twincer<sup>®</sup> and the Turbuhaler<sup>®</sup> were measured with the same laser diffraction apparatus (100 mm lens), and the inhalers were connected to a previously described inhaler adapter (INHALER 2000, Sympatec; de Boer et al., 2002a). Start of the measurements was triggered on the optical concentration in the aerosol cloud (0.2% on channel 30), and the measurements were stopped either after the signal decreased to a value lower than 0.2% on the same channel, or after 3 s of real measurement time.

For cascade impactor analyses of the aerosol from optimised (machined) concepts, a four stage impactor with glass constructed induction port was used. Fractions deposited on the impactor stages were allowed to dissolve for at least one hour in 20 ml of demineralised water (per stage) and the solutions were analysed with a slightly modified folin phenol method as described by Lowry et al. (1951). Cascade impactor results given are the mean of two series of two inhalations each. For the calculation of the theoretical cut-off diameters of the impactor stages, a density of 1400 kg/m<sup>3</sup> for the colistin sulfomethate was used.

## 3. Results and discussion

### 3.1. De-agglomeration efficiency of the Twincer<sup>®</sup>

The mechanisms of powder de-agglomeration in a classifier have been described before (de Boer et al., 2003; 2005a). Fig. 11.3 shows the size distribution of the aerosol from the Twincer<sup>®</sup> concept presented in Fig. 11.2 for budesonide spherical pellets (taken from the Pulmicort<sup>®</sup> 200 Turbuhaler<sup>®</sup>) in comparison with that for the Turbuhaler<sup>®</sup> at 1 and 4 kPa. The dose from the Twincer<sup>®</sup> was 2 mg with 2 mg sweeper crystals (size fraction 150-200  $\mu\text{m}$ ). This is 20 times higher as the nominal dose from the Turbuhaler<sup>®</sup>. Nevertheless, the de-agglomeration efficiency of the Twincer<sup>®</sup> for this relatively high dose at 1 kPa is already as good as that of the Turbuhaler<sup>®</sup> at 4 kPa. For comparison, the primary size distribution of the drug obtained from RODOS dispersion at 5 bar is also shown in Fig. 11.3. The role of sweeper crystals in a classifier as powder de-agglomeration principle has been described before (de Boer et al., 2002b).

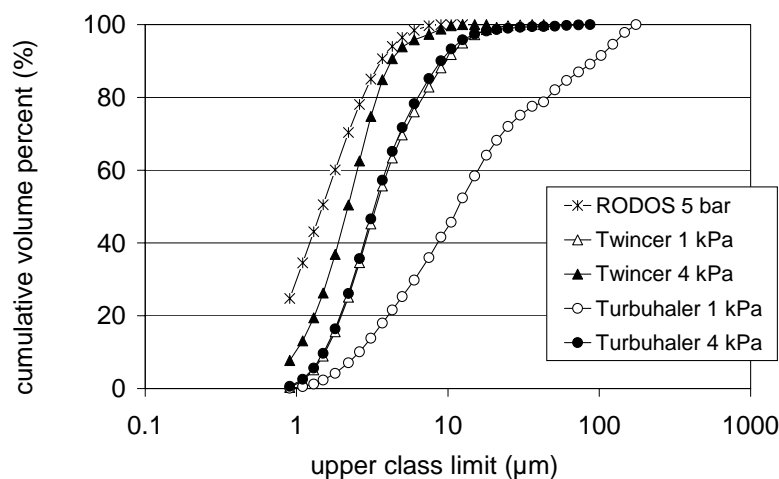


Figure 11.3. Size distribution of the aerosol (from laser diffraction analysis) produced by the Twincer<sup>®</sup> concept in Fig. 2 for budesonide soft spherical pellets (used in the Turbuhaler<sup>®</sup>) at 1 and 4 kPa in comparison with the size distributions from the Turbuhaler<sup>®</sup> and the RODOS dry powder disperser. The dose from the Turbuhaler<sup>®</sup> was 0.1 mg (pure drug); the total dose from the Twincer<sup>®</sup> was 4 mg (mixture with 2 mg drug and 2 mg sweeper crystals 150-200  $\mu\text{m}$ ). Mean of five doses.

### 3.2. Effect of dose weight on the size distribution of the aerosol

The effect of the dose weight on the size distribution of the aerosol from different Twincer<sup>®</sup> concepts at 4 kPa is shown in Fig. 11.4A for micronised colistin sulfomethate. All concepts used for the experiments had two parallel classifiers with a circular shape and three air supply channels, as shown in Fig. 11.1. The differences between the concepts were confined to different diameters of the classifier chambers (11 mm for concept 1 and 15 mm for the concepts 2 and 3), different heights of the rim around the discharge holes (1.5 and 2 mm for concepts 2 and 3 respectively) and different amounts of bypass air entering the discharge channels. For comparison, the  $X_{50}$  (closed symbol) and  $X_{90}$ -value (open symbol) of the primary particles (obtained with RODOS dispersion at 3 bar) are shown on the abscissa (0 mg). The dose weights are for the pure drug without sweeper crystals. For concept 1, the additional amount of sweeper (fraction 250-300  $\mu\text{m}$ ) was 15%; for the concepts 2 and 3 the same sweeper weight of 2 mg was used for all dose weights (fraction 150-200  $\mu\text{m}$ ). Fig. 4A shows that the size distribution of the aerosol cloud from the concepts 2 and 3 is hardly influenced by the dose weight up to (and including) 25 mg of pure micronised drug. The  $X_{50}$ -value is constant, which is also proof for the excellent dispersion reproducibility of the inhaler. For concept 1, only the  $X_{90}$ -value increases slightly with increasing dose weight and the magnitude of the increase appears to depend on whether sweeper crystals are used or not. The reason for the increase in  $X_{90}$  for concept 1 is the relatively short residence time of the powder in the classifier for this concept. As a result, part of the larger drug agglomerates may already be discharged from the classifier before complete de-agglomeration could occur. The effect becomes first noticeable at higher classifier payloads when agglomerates crowd each other out. When the residence time is slightly increased and large particle retention is improved (as in concepts 2 and 3), the fraction of the drug released as small agglomerates becomes almost negligible, also at higher dose weights. This is shown in Fig. 11.4B for concept 2. The size distributions at 8 and 25 mg are exactly the same, which confirms that the de-agglomeration is good at all payloads, but a minor secondary peak of small agglomerates (with a peak around 9  $\mu\text{m}$ ) occurs at the highest payload. These agglomerates represent approximately 5% of the total dose.



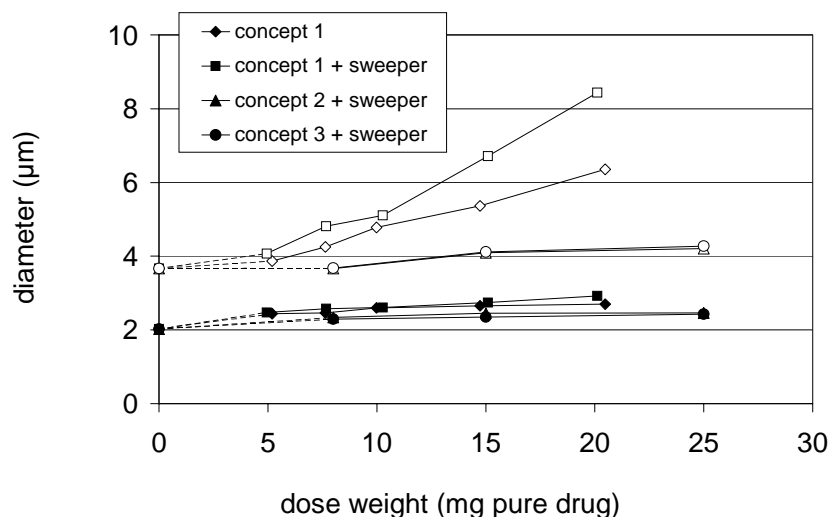


Figure 11.4A. Size distributions of the aerosols for colistin sulfomethate at 4 kPa from three different Twincer<sup>®</sup> concepts ( $X_{50}$ , closed symbols and  $X_{90}$  as open symbols from laser diffraction analysis), as function of the dose weight. Each data point is the mean of two experiments; the spread is too small to be indicated.

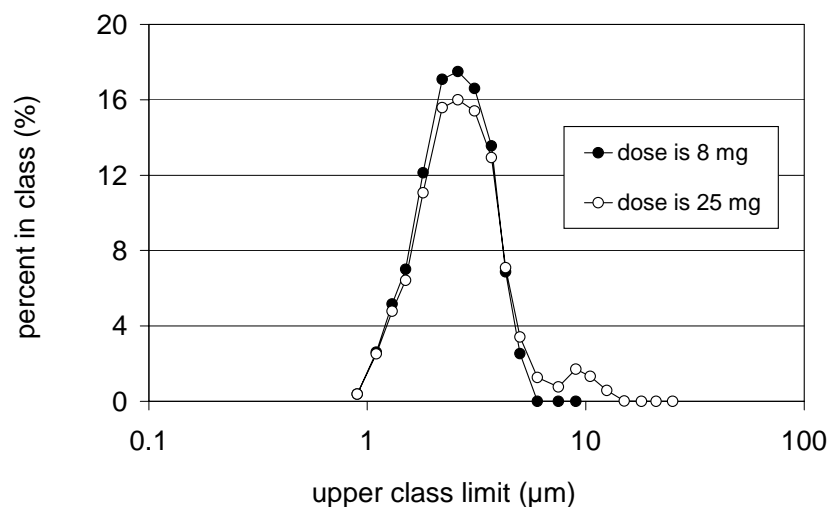


Figure 11.4B. Volume frequency distribution at 4 kPa for concept 2 in Fig. 4A for two different dose weights of 8 and 25 mg of pure drug.

### 3.3. Reduction of the inhaler losses and retention of sweeper crystals

One of the problems to solve when high drug doses are dispersed with a high efficiency is the inhaler accumulation. Particularly when a classifier type of de-agglomeration principle is used, fine particle adhesion onto the cylindrical classifier wall may be substantial, unless the surface area of this wall can be reduced (e.g. by increasing the number of air supply channels: de Boer et al., 2005a), or sweeper crystals are added to the drug formulation that wipe adhering drug particles off the classifier wall during inhalation (de Boer et al., 2002b). Surrounding a classifier with a large number of tangential air channels has the consequence

that more space must be provided for the total classifier arrangement. With two parallel classifiers side by side in the same plane, this increases the dimensions of the inhaler quite substantially. For that reason, the use of sweeper crystals seems to be a better option, particularly for a single use device for which retained crystals do not have to be removed from the classifiers after use, as the complete inhaler is disposed. The mass fraction of sweeper crystals in the formulation can be kept relatively low to obtain the desired effect, whereas the crystals may be retained in the classifier during inhalation to avoid deposition in the upper respiratory tract. The effect of sweeper action on total inhaler accumulation at 4 kPa for micronised colistin sulfomethate is shown in Fig. 11.5 as function of the dose weight. Without sweeper crystals the total inhaler losses are around 30% of the total drug dose. With 15% (w/w) sweeper crystals (size fraction 250-355  $\mu\text{m}$ ) in the formulation, the losses are reduced to approximately 20% of the drug dose at all dose weights. The reduction is the same when other sweeper fractions in the same weight percentages are used. The remaining fine particle losses for this concept were found in the mouthpiece channel, particularly against the top plate above the discharge holes where the sweeper crystals are not effective.

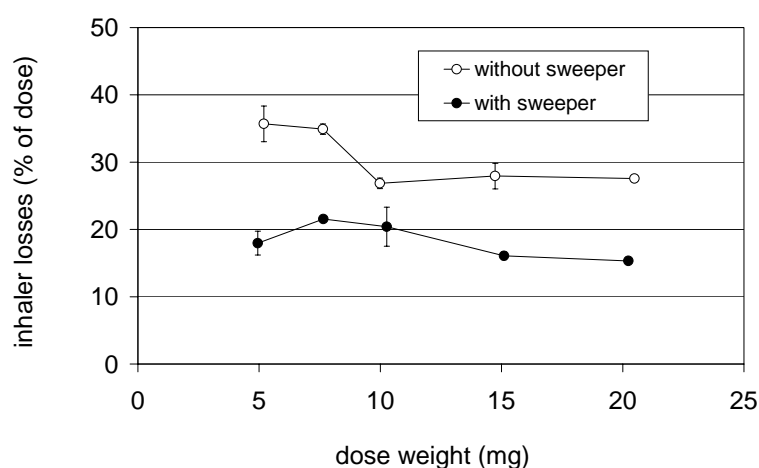


Figure 11.5. Inhaler accumulation for colistin sulfomethate at 4 kPa of concept 1 in Fig. 5A with and without (15% w/w) sweeper lactose (250-355  $\mu\text{m}$  from Pharmatose 80M) as function of the dose weight (weight is for drug plus sweeper).

The addition of sweeper crystals to the formulation could be disadvantageous, as deposition of these crystals in the upper respiratory tract may cause irritation in the patient. In contrast with a single air classifier having the same longitudinal axis as the inhaler mouthpiece, large (carrier or sweeper) particles from the Twincer<sup>®</sup> are not deposited in the front of the mouth by centrifugal action (de Boer et al., 2005a), but rather in the oropharynx. Therefore, sweeper retention may be desired. Fig. 11.6 shows the retention efficiency of Twincer<sup>®</sup> concept 1 (in Fig. 11.4A) with different configurations for the discharge channel and for two different sweeper size fractions at 4 kPa. For all configurations, the retention of a coarse sweeper fraction (250-355  $\mu\text{m}$ ) is rather complete, but the retention efficiency for a smaller fraction (63-100  $\mu\text{m}$ ) depends particularly on the distance between the rim around the discharge holes and the bottom of the classifier chamber, which is determined by the height of the rim. This enables control of the degree of passage for the sweeper crystals without influencing the de-agglomeration efficiency, as shown in Fig. 11.4A where the rim height between concepts 2 and 3 is varied over the same distance as between the concepts D5/2 and

D5/1.5 in Fig. 11.6. There is neither a noticeable influence on the total inhaler resistance, which is exactly the same ( $0.034 \text{ kPa}^{0.5} \cdot \text{min} \cdot \text{l}_N^{-1}$ ) for all configurations shown in Fig. 11.6.

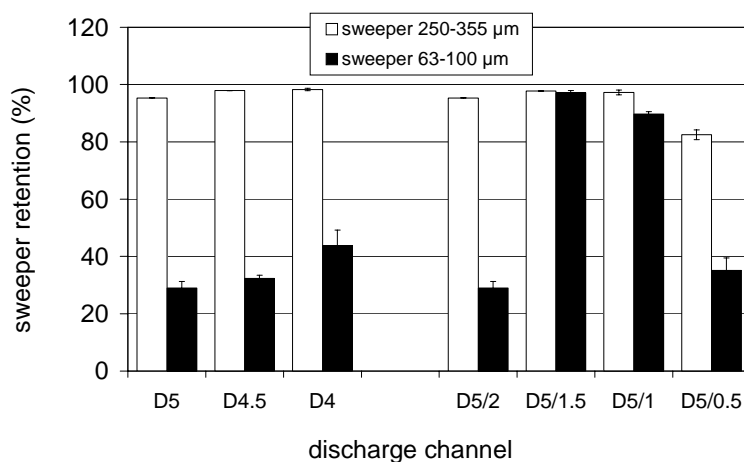


Figure 11.6. Sweeper retention (as percent of dose weight) at 4 kPa for two different lactose size fractions by concept 1 in Fig. 4A with different configurations for the discharge channel. Numbers (on the ordinate) in combination with the letter D refer to the diameter of the discharge channel (mm). Numbers following the slash mark refer to the height of the slit between the discharge channel and the bottom of the classifier chamber. Mean of two experiments; dose weight (sweeper only) is 25 mg.

### 3.4. Effect of the inspiratory effort on the fine particle fraction (fpf)

The effect of the inspiratory effort (1 or 4 kPa) on the in vitro deposition of colistin sulfomethate from the Twincer<sup>®</sup> concepts C2 and C3 in a multi stage impactor is shown in Fig. 11.7. For these concepts, 1 and 4 kPa correspond with 30 and 60  $\text{l}_N/\text{min}$  respectively. In Fig. 11.7 cumulative subfractions of particles are indicated within the size fraction  $< 7.5 \mu\text{m}$ . The total fine particle fractions ( $< 7.5 \mu\text{m}$ ) are of the same order of magnitude for both concepts, but the distributions of particles within these fractions are quite different at 4 kPa. The difference is highly reproducible, as can be concluded from the spread bars which are approximately the same for each of the cumulative subfractions up to  $7.5 \mu\text{m}$ . The difference in subfractions is the result of a difference in the (theoretical) cut-off diameters of the classifiers, which are  $13.6 \mu\text{m}$  at 30  $\text{l}/\text{min}$  and  $9.6 \mu\text{m}$  at 60  $\text{l}/\text{min}$  for concept 2 (for colistin sulfomethate). In this classifier concept 2 (small cut-off diameters), drug agglomerates remain circulating in the classifier until they have become disintegrated almost completely, which is within the first second of inhalation for the colistin sulfomethate sample used in the experiments. For concept 3, the theoretical cut-off diameters for the same drug are  $19.2 \mu\text{m}$  and  $13.6 \mu\text{m}$  at 30 and 60  $\text{l}/\text{min}$  respectively. The increased cut-off values enable more (small) drug agglomerates to be discharged from this classifier concept 3, which increases particularly the  $X_{90}$ -value of the emitted aerosol. They also influence the size distribution within the fine particle fraction ( $< 7.5 \mu\text{m}$  in Fig. 7). Lower subfractions  $< 1.5$  and  $1.5$  to  $3 \mu\text{m}$  for concept C3 are compensated by higher subfractions 3 to 5 and 5 to  $7.5 \mu\text{m}$  (compared to C2). The possibility to vary fpf at the same inspiratory effort and for the same type of drug could have potential for fine tuning of the lung deposition in patients with different lung anatomies and morphologies.

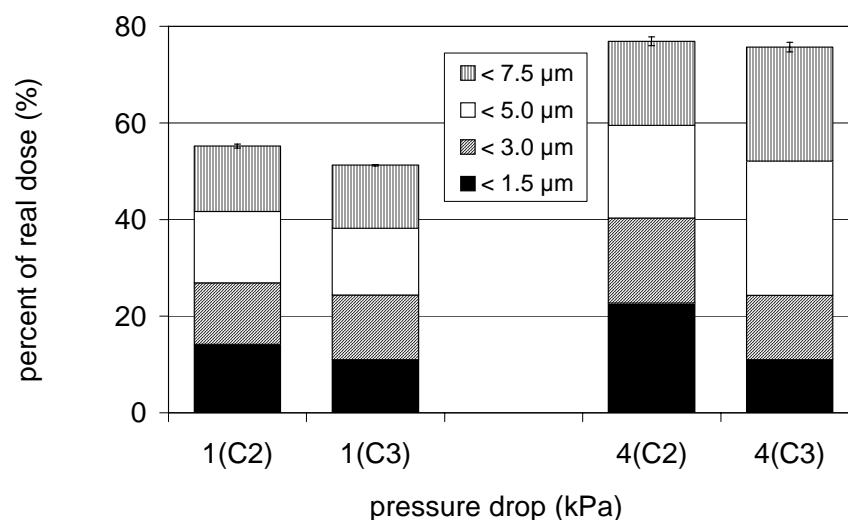


Figure 11.7. Fine particle fractions from concepts C2 and C3 collected in a four stage impactor 1 and 4 kPa. The dose is 8 mg colistin sulfomethate with 2 mg sweeper crystals (size fraction 150-200  $\mu\text{m}$ ). Each data given is the mean of two series of inhalations (three doses per series).

Fig. 11.7 shows that the fine particle fraction  $< 7.5 \mu\text{m}$  is considerably higher at 4 kPa than that at 1 kPa (on average 76.3% and 53.3% of the real dose for both concepts respectively). This is not primarily the result of an improved de-agglomeration efficiency with increasing flow rate through the inhaler. The main reason is a much higher inhaler accumulation at 1 kPa. As shown in Fig. 11.5, the inhaler losses of the concept depicted in Fig. 2 can be reduced to 20% of the real dose by adding a small fraction of sweeper crystals. By adding a minor bypass flow to the discharge channels additionally, the inhaler losses can be further reduced to 5 - 10% of the real dose at 4 kPa (5.6% for the experiments presented in Fig. 11.7). The bypass flow is directed over the discharge holes, which deflects the powder flow from these holes and reduces particle collision with the top plate. At 1 kPa, corresponding with 30 l/min, the air velocity of the bypass flow is insufficiently high, which makes further improvement necessary (inhaler losses are 25.3% for the experiments in Fig. 11.7). The difference in inhaler losses between 1 and 4 kPa (19.7%) explains fairly well the difference in fine particle fraction  $< 7.5 \mu\text{m}$  (23.0% in Fig. 11.7).

Fig. 11.8 confirms that the size distributions of the aerosol (from laser diffraction analysis) from concept 2 in Fig. 11.7 differ only slightly between the different pressure drops. The peaks of the volume frequency distribution curves appear at exactly the same diameter for the aerosols generated at 1, 2 and 4 kPa. The difference between the curves is confined to a small difference in the volume of the larger particles. For comparison, the size distributions from RODOS dispersion at 0.5 bar are also given in Fig. 11.8. A difference between the RODOS and the Twincer<sup>®</sup> exists only for the finest particles ( $< 1.5 \mu\text{m}$ ), which can not be dispersed completely into primary entities by the Twincer<sup>®</sup>. In contrast, the Twincer<sup>®</sup> disintegrates larger drug agglomerates more effectively, particularly after a slight pressure has been applied to the powder (RODOS 0.5 bar indicated with asterisks). A slight compression of the powder (into a coherent cake) is necessary to fill large powder weights in the dose compartments of the Twincer<sup>®</sup>. In spite of a 12.5 times lower dispersion pressure (0.5 bar versus 4 kPa, which equals 0.04 bar), the Twincer<sup>®</sup> de-agglomerates such a powder lump more effectively than the RODOS disperser.

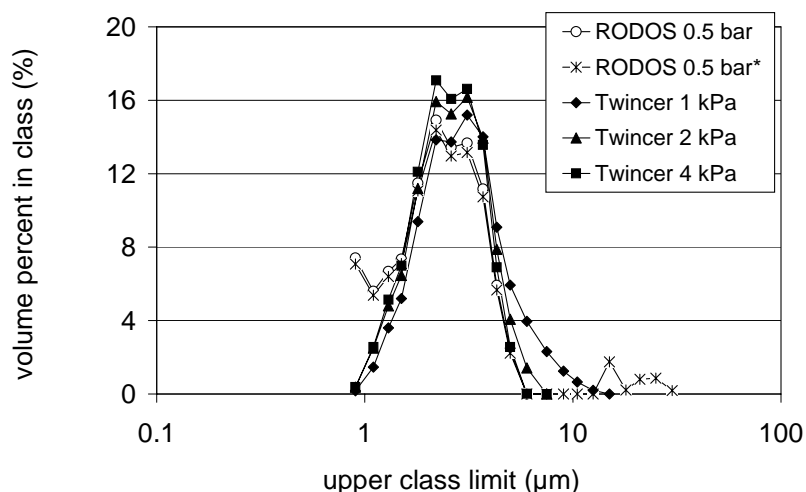


Figure 11.8. Volume frequency distribution curves for the aerosol from Twincer<sup>®</sup>-concept 2 (in Fig. 11.4A) at 1, 2 and 4 kPa (8 mg colistin sulfomethate + 2 mg sweeper) in comparison with the size distributions from RODOS dispersion at 0.5 and 3 bar. Mean of two series per experiment. RODOS 0.5 bar\*: drug mixture is slightly compressed (see text).

In a previous study, it has been discussed that an increasing FPF with increasing flow rate is beneficial because it compensates for a shift in deposition towards higher airways (de Boer et al., 2005b). For the Twincer<sup>®</sup>, an increasing FPF with the inspiratory effort above 1 kPa is not possible after the drug accumulations in the inhaler at this pressure drop (corresponding with approx. 30 l/min) have been reduced to that at 4 kPa (5-6% of the real dose for colistin sulfomethate). Instead, limitation of the flow rate to a narrow range of values may be desired.

### 3.5. Discrepancy between the laser diffraction and cascade impactor results

There exists a discrepancy between the results from cascade impactor analysis (cia) and those from laser diffraction analysis (lda) for the same Twincer<sup>®</sup> with the same formulation at the same flow rate. For instance, the results in Fig. 11.8 from lda suggest that all particles in the colistin sulfomethate aerosol from the Twincer are smaller than 6 µm at 2 and 4 kPa. In contrast, cia produces a size distribution in which 76% is smaller than 7.5 µm (Fig. 11.7) at the same pressure drop. These differences can be explained partly by differences in procedures (e.g. laser diffraction diameter compared with aerodynamic diameter). There is also a contribution to the difference from the fact that cia-results are presented as percent of the total dose, whereas lda-results are given as percent of the emitted dose. Corrections can be made for these differences however, and this makes clear the major cause is not in the procedures and/or computations, but in the equipment used. Particularly imperfections in the impactor cut-off values may have played a major role (Hinds, 1982) and the steepness of the cut-off curves may have been reduced even further by the high particle concentrations in the aerosol cloud. As a result, the size distribution obtained from cia is much wider than that from lda. After correction for the differences in procedures, the fraction of fine particles (< 1.5 µm) in the aerosol from the Twincer<sup>®</sup> obtained with cia at 4 kPa (26.4%) is still much higher than that obtained from RODOS dispersion (only 18.4% at 5 bar). This makes the cascade impactor result highly arguable and the discrepancy between both techniques will be subject of a separate study.

#### 4. Conclusions

The side by side arrangement of classifiers in the same planar housing has many advantages. It enables to give the inhaler a slim design with the shape and approximate size of a credit card. The total height can be reduced to 1 cm or even less. The transversal connection of the discharge channels to the classifier outlet holes eliminates the tangential component in the air flow from the mouthpiece, which reduces the mouth deposition. Therefore, sheath flow is not necessary (de Boer et al., 2005a), and a larger portion of the total flow through the inhaler can be directed through the classifiers which increases the de-agglomeration efficiency. Part of the flow may also be used to reduce the drug particle adhesion in the discharge channel. The simple design reduces the production costs, as the three plate-like parts (with the blister) can simply be stacked and clicked together. This makes the inhaler suitable for single use, which has several advantages. For instance, it prevents contamination and the development of antibiotic resistant bacteria, or inhaler pollution (e.g. for hygroscopic drug formulations). Moreover, it makes the inhaler suitable for single use therapy, as for instance pulmonary vaccination.

Although the machined copies of the Twincer<sup>®</sup> used for this in vitro study with colistin sulfomethate were not fully optimised yet with respect to air flow resistance, powder entrainment from the dose system and inhaler accumulations, it has been shown that high fine particle fractions can be obtained as the result of an extremely high de-agglomeration efficiency. Special particle engineering processes to reduce the interparticulate forces are not necessary. A twenty-fold dose can be dispersed with the same efficiency at 1 kPa with the Twincer<sup>®</sup> as at 4 kPa with the Turbuhaler<sup>®</sup>. For all prototypes used in this study, the size distribution in the aerosol (at 4 kPa) is largely independent of the dose weight between 0 and 25 mg. It is inherent in the dispersion of micronised powders in a classifier type of de-agglomeration principle that a certain fraction of the particles is lost by adhesion to the classifier walls. However, the addition of 10 - 15% sweeper crystals to the formulation (in a size fraction larger than 50  $\mu\text{m}$ ) appears to be effective in reducing this accumulation to less than 5% of the total dose at all flow rates for colistin sulfomethate. The remaining inhaler losses (approx. 20% of the dose at 4 kPa) are found in the discharge channels. However, by directing bypass flows around the discharge holes, these losses can be further reduced to a total inhaler accumulation of only 5-6% at 4 kPa. The Twincer<sup>®</sup> classifiers can be modified to retain the sweeper crystals with high efficiency (>95%) in order to minimise excipient particle deposition in the (upper) respiratory tract. Similar modifications can also be used to control the size distribution within the fine particle fraction (< 7.5  $\mu\text{m}$ ) from the inhaler to a certain extent for the same drug at the same flow rate. This, by releasing either primary particles only or a mixture of primary particles and small drug agglomerates.

With the current Twincer<sup>®</sup> design, a powder dose of 25 mg of pure drug can effectively be de-agglomerated. Further optimisation of the design could raise this to a dose of 50 mg. The high de-agglomeration efficacy makes the inhaler suitable for highly cohesive formulations, such as solid dispersions of drugs in sugar glasses. Even for these formulations, battery powered dispersion systems or pressurised gas canisters, as for instance described by Young et al. (2004) are not necessary. The good dispersion of high drug doses, the good moisture protection of the drug formulation in a blister, and the disposable inhaler design, make the Twincer<sup>®</sup> also suitable for other applications, like the administration of rhDNase in CF or vaccines. It has already been shown that the pulmonary route may be effective for vaccines against measles (LiCalsi et al., 1999; Dilraj et al., 2000) and influenza (Jemski and Walker, 1976).

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