Design and in vitro performance testing of multiple air classifier technology in a new disposable inhaler concept (Twincer®) for high powder doses

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Summary

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 dispersion of large amounts of micronised powder (up to 25 mg). $X_{50}$-values of the aerosol from laser diffraction analysis obtained with the Twincer® disposable inhaler concept (containing multiple air classifier technology) are practically the same as that for the pure drug in the range of dose weights between 0 and 25 mg. Only for the highest dose weights, a minor fraction (5–7.5%) of small agglomerates (5–15 μm) is released from the inhaler. Moreover, the size distribution of the aerosol is practically the same at 1 and 4 kPa. Cascade impactor results confirm the good performance of the multiple classifier concept. 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 total inhaler losses for colistimethate sodium to less than 5–6% at 4 kPa. The classifiers can be designed to retain these crystals with more than 95% efficiency.
Introduction

In the past decade, a great interest has been developed in the pulmonary administration of high drug doses, e.g. for systemically active substances that cannot 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 Follinsbee, 1997; Groneberg et al., 2003). The preferable drug particle size for deposition in the small airways is between 1 and 5 μm under the conditions of quiet breathing and a certain period of breath hold (Gerrity, 1990; Martonen and Katz, 1993; Schultz, 1998).

Many 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 mostly, such powders are highly hygroscopic and cohesive. All these factors contribute to a low (and highly variable) bioavailability, as reported for instance for insulin until now. 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 the antibiotics, given 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 influenza 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 Deventer 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), colistimethate sodium (Li et al., 2001) and tobramycin (Le Brun et al., 1999). Conventional nebulisation of the high doses (e.g. 160 mg for gentamicin and colistimethate sodium and 300 mg for tobramycin), may require up to 30 minutes. This influences the quality of life and it is disadvantageous from the viewpoint of patient adherence to treatment.

An alternative for wet nebulisation is dry powder inhalation. Dry powder inhalers for gentamicin (Goldman et al., 1990; Crowther Labiris et al., 1999), colistin sulfate (Le Brun et al., 2002), colistimethate sodium (Flynn et al., 2000) and tobramycin sulfate (Newhouse et al., 2003) have been presented with varying success. These studies have shown that sputum (or plasma) concentrations and lung depositions may be comparable to those achieved with nebulisation, but the inhaled doses from dry powder inhalers were rather high so far. They varied from 160
to 180 mg for gentamicin, 150 mg for tobramycin sulfate (PulmoSphere formulation), 30–150 mg for colistimethate sodium 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 were for the pure drug, except for the PulmoSphere formulation, which contained 10% excipient. As a result, inhalation of a relatively large number of powder quantities for a single dose was necessary, varying from 3 (for colistin sulfate) to 32 (for gentamicin). Not even particle engineering (like processing of tobramycin sulfate into PulmoSphere) appeared to be sufficiently effective to reduce the number of inhalations (Newhouse et al., 2003).

The aim of this study was to develop a highly effective, so-called passive (i.e. breath driven) powder de-agglomeration principle for a new disposable inhaler concept which enables the pulmonary administration of high drug doses in one or two inhalation manoeuvres. The application is primarily for antibiotics and for sugar glass formulations containing therapeutic proteins (or lipophilic drugs), but the inhaler may also be used for other drugs, like for instance medication that has to be given only once (e.g. vaccines). The de-agglomeration principle (multiple air classifier technology) has been designed to produce a high fine particle fraction already at a relatively low inspiratory effort without using particle-engineered technologies. This will make it possible to inhale slowly and to minimise throat and upper tract deposition. Another objective was to minimise the amount of inert excipient in the inhalation powder, which (in combination with efficient excipient retention by the inhaler) reduces the amount of powder to be inhaled.

Materials and methods

The disposable Twincer®, multiple classifier dry powder inhaler

The design of the disposable multi classifier dry powder inhaler is shown in Fig. 1. Basically, the inhaler consists of three plate-like parts and a blister strip for the powder formulation with the micronised drug. The plate-like parts have various projections and depressions which constitute the air flow passages and the blister chamber when the parts are assembled, as shown and explained more in detail by de Boer et al. (2004). The powder formulation is stored in a blister which has a long cover foil. This cover foil 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 and the inlet to this channel (Fig. 1). 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, which are circular depressions in the bottom plate (classifier plate) of the inhaler. The classifiers shown in Fig. 1 have two additional air channels each (to maintain a stable tangential flow pattern inside the classifiers), but there may be different numbers of such channels. 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., 2004). For the
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Twincer® concept depicted in Fig. 1, the classifier discharge holes (in the discharge plate) are circular. Around each hole (on the bottom side of the discharge plate facing the classifier plate) there is a circular 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 rims around the discharge holes (in relation to the depth of the classifier chamber) 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 holes are connected with two discharge channels ending in the mouthpiece channel of the inhaler which ends (for the prototype tested) as a straight narrow opening. Bypass channels around the discharge holes are used to reduce the inhaler accumulations and to control the total inhaler resistance.

In this study, only the de-agglomeration efficiency of the multiple classifier principle has been tested. Optimisation of the entire inhaler design (including the mouthpiece, which controls the aerosol discharge flow in the oral cavity) was not (yet) the objective.

The example shown in Fig. 1 is the basic design of the Twincer® multiple classifier inhaler. Various concepts with different classifier designs for different drug formulations have been constructed and tested. Fig. 2A shows the machined concept used for a proof of principle with colistimethate sodium in CF patients and healthy volunteers, of which the results have been presented by Westerman et al., 2007a, 2007b). This concept has no blister, but two different

Figure 1  Presentation of the Twincer® 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. Relevant inhaler parts (and functions) discussed in the text are indicated in the drawing.
dose compartments (filled manually) which can be connected with the powder channel by means of a slide.

Figure 2  A. Presentation of the (machined) concept used for a proof of principle to administer 2 x 12.5 mg colistimethate sodium to 7 healthy volunteers and 10 CF patients. The concept has no blister, but two dose compartments for the drug formulation that can be connected with the air inlet (hole) and the powder channel by means of a slide.

B. Presentation of a first moulded prototype of the Twincer® (with blister; not visible) to be used for a patient study with cyclosporine.

dose compartments (filled manually) which can be connected with the powder channel by means of a slide. Fig. 2B shows a first moulded prototype containing a single blister (300mm³) to be used for a patient study with cyclosporine.

Materials
Micronised colistimethate sodium was purchased from Alpharma (Copenhagen, Denmark). Characteristic values for the size distribution (obtained from laser diffraction analysis using RODOS dispersion at 3 bar) after micronisation (see Section 2.3) are $X_{10} = 0.88 \, \mu m$; $X_{50} = 1.99 \, \mu m$. 
μm; X_{90} = 3.53 μm and X_{100} = 5.00 μm. Pharmatose 110M and 80M (starting materials for the
preparation of special size fractions of sweater crystals) were supplied by DMV International
(Veghel, The Netherlands). A Pulmicort® 200 Turbuhaler® (reference device) was obtained from
the local pharmacist. All Twincer® devices used in this study were machined devices, similar
to that shown in Fig. 2A. They were constructed by the research workshop of the Faculty of
Medicine (University of Groningen).

**Methods**

For the micronisation of the colistimethate sodium to the desired size distribution for inhalation,
a spiral jet mill with 0.8mm nozzle (50 AS, Alpine, Augsburg, Germany) was used. Lactose size
fractions (sweater crystals) of 63–100; 150–200 and 250–355 μm 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). Sweater crystals and colistimethate
sodium were either mixed (10 min) in the indicated quantities, 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(s) of the Twincer®.

Size distributions of the starting materials (drugs and sweater fractions) 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. Computations of diffraction data (obtained with a 100
mm lens for the drug) into particle size distributions were made with the Fraunhofer theory. For
the sweater fractions 200 and 500 mm lenses were used. The size distributions of the aerosols
from the Twincer® and the Turbuhaler® were measured with the same laser diffraction appara-
tus (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 the *in vitro* deposition of the aerosol from two different Twincer® concepts, a four stage
impactor with glass constructed induction port was used (Hallworth and Andrews, 1976). Fractions
deposited on the impactor stages were allowed to dissolve for at least 1 h in 20 ml of
demineralised water (per stage) and the solutions were analysed with a slightly modified folin
phenol method as described by Lowry (Lowry et al., 1951). Cascade impactor results given are
the mean of two series of three inhalations each. For the calculation of the theoretical cut-off
diameters of the impactor stages, a density of 1400 kg/m³ for the colistimethate sodium was
used.
Results and discussion

The de-agglomeration efficiency of the Twincer®
The mechanisms of powder deagglomeration in an air classifier have been described before (De Boer et al., 2003). Fig. 3 shows the size distribution of the aerosol from the Twincer® concept presented in Fig. 2A for budesonide spherical pellets (taken from the Pulmicort® 200 Turbuhaler®) in comparison with that from the Turbuhaler® at 1 and 4 kPa. The dose from the Twincer® was 2 mg with 2 mg sweeper crystals (size fraction 150–200 μm). This is 10 times higher than the nominal dose from the Turbuhaler®. Nevertheless, the deagglomeration efficiency of the Twincer® for this relatively high dose at 1 kpa is already as good as that of the Turbuhaler® at 4 kPa. For comparison, the primary size distribution of the drug obtained from RODOS dispersion at 5 bar is also shown in Fig. 3. The role of sweeper crystals in a classifier as powder de-agglomeration principle has been described before (De Boer et al., 2002b). They remove adhering drug particles from the inner walls of the classifier chambers during inhalation and reduce the inhaler losses.

The 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® concepts at 4 kPa is shown in Fig. 4A for micronised colistimethate sodium. All concepts used for the experiments had two parallel classifiers with a circular shape and each classifier had one...
Design and in vitro performance testing of multiple air classifier technology in the Twincer® powder channel and two additional air channels, as shown in Fig. 1. The differences between the concepts were confined to different diameters for the classifier chambers (11 mm for concept 1 and 15 mm for the concepts 2 and 3), different heights of the rims around the discharge holes (1.5 mm for concept 2, and 2 mm for concepts 1 and 3) and slightly different amounts of bypass air entering the mouthpiece channel along the discharge holes. For comparison, the

**Figure 4**  A. Size distributions of the aerosols for colistimethate sodium at 4 kPa from three different Twincer® concepts as function of the dose weight (pure drug). Closed symbols are for $X_{50}$- and open symbols for $X_{90}$-values from laser diffraction analysis; similar symbols (open and closed) refer to the same concept. Each data point is the mean of two experiments; the spread is too small to be indicated. B. 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.
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\( X_{50} \) (closed symbol) and \( X_{90} \)-value (open symbol) of the primary drug particles (obtained with RODOS dispersion at 3 bar) are shown on the abscissa. The dose weights on the ordinate are for the pure drug without sweeper crystals. For concept 1, the additional amount of sweeper (fraction 250–300 μm) was 15% (mixed with the drug); for the concepts 2 and 3 the same sweeper weight of 2 mg (fraction 150–200 μm) was used for all dose weights (drug and sweeper crystals weighed separately into the dose compartments). 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 and, which is also proof for the excellent dispersion reproducibility of the inhaler, only 10% higher than the \( X_{50} \) of the primary particles from RODOS dispersion. 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, the diameter of the classifier chamber is relatively small compared to the diameter of the discharge hole. As a result, part of the larger drug agglomerates may already be discharged from the classifier before de-agglomeration is complete. The effect becomes first noticeable at higher classifier payloads when agglomerates crowd each other out, particularly when sweeper crystals are also present in the classifier. 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. 4B for concept 2. The particle size distributions from 8 to 25 mg doses 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 μm) occurs at the highest payload. These agglomerates represent only approximately 5% of the total dose.

**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 additional air channels: De Boer et al., 2004) or sweeper crystals are added to the drug formulation. 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 inhalation, since 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 colistimethate sodium is shown in Fig. 5 for one particular Twincer® concept 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 μm) in the formulation, the losses are reduced to approximately 20% of the drug dose at all dose weights. The reduction is the same for this type of drug 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. Reduction of these losses therefore requires other means, such as the arrangement of bypass flows directing the discharge flow from the classifiers.

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® are not deposited in the front of the mouth by centrifugal action, but rather in the oropharynx. Therefore, sweeper retention may be desired. Fig. 6 shows the retention efficiency of Twincer® concept 1 (from Fig. 4A) with different classifier discharge holes (with diameters varying between 4 and 5 mm) and for two different sweeper size fractions at 4 kPa. For all discharge holes, the retention of a coarse sweeper fraction (250–355 μm) is rather complete, but the retention efficiency for a smaller fraction (63–100 μm) depends particularly on the distance between the rim around the discharge holes and the bottom of the
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classifier chamber (varied between 0.5 and 2.5 mm), which is determined by the height of the rim. This enables control of the degree of passage for the sweeper crystals without influencing the deagglomeration efficiency, as shown in Fig. 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. 6. There is neither a noticeable influence on the total inhaler resistance from the height of the rim, which is exactly the same 0.034 kPa\(^{0.5}\) \(\text{min l}_N^{-1}\) for all configurations shown in Fig. 6.

**Figure 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 hole (mm). Numbers following the slash mark refer to the height of the slit between the rim around the discharge hole and the bottom of the classifier chamber. Mean of two experiments; dose weight (sweeper only) is 25 mg.

classifier chamber (varied between 0.5 and 2.5 mm), which is determined by the height of the rim. This enables control of the degree of passage for the sweeper crystals without influencing the deagglomeration efficiency, as shown in Fig. 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. 6. There is neither a noticeable influence on the total inhaler resistance from the height of the rim, which is exactly the same 0.034 kPa\(^{0.5}\) \(\text{min l}_N^{-1}\) for all configurations shown in Fig. 6.

**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 colistimethate sodium from the Twincer® concepts 2 and 3 in Fig. 4A in a multi stage impactor is shown in Fig. 7. For these concepts (referred to as C2 and C3), 1 and 4 kPa correspond with 30 and 60 l/min, respectively. In Fig. 7 cumulative subfractions of particles are indicated within the size fraction <5 \(\mu\text{m}\). The total fine particle fractions (<5 \(\mu\text{m}\)) are of the same order of magnitude for both concepts, but the distributions of particles within these fractions are different, particularly 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 5 \(\mu\text{m}\). The difference in the subfractions may be the result of a difference in the (theoretical) cut-off diameters of the classifiers, which are 13.6 and 9.6 \(\mu\text{m}\) for concept 2 and 19.2 and 13.6 \(\mu\text{m}\) for concept 3 at 30 and 60 l/min, respectively (for colistimethate sodium).
Fig. 7 shows that the fine particle fraction <5 μm is considerably higher at 4 kPa than at 1 kPa (on average 55.8% and 40.0% 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. 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 also a minor bypass flow to the discharge channels, the inhaler losses can be further reduced to <10% of the real dose at 4 kPa (5–7% for the experiments presented in Fig. 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 however, which makes further concept improvement necessary (inhaler losses are on average 25.3 and 5.8% for the experiments in Fig. 7 at 1 and 4 kPa, respectively). The difference in inhaler losses between 1 and 4 kPa (19.5%) explains fairly well the difference in fine particle fraction <5 μm (15.8% in Fig. 7). Less than 5% of the total dose has been deposited on the stages 1 and 2 of the impactor and less than 8% in the induction port to the impactor (the same for both pressure drops). The ‘missing’ 25% of the dose (also the same for both pressure drops) has been released from the inhaler within the size fraction 5–8.5 μm (at 4 kPa) and 5–12 μm (at 1 kPa), respectively. In this comparison, the upper sizes of the ‘missing’ fractions equal the cut points of the second impactor stage at 1 and 4 kPa.

Fig. 8 confirms that the size distributions of the aerosol (from laser diffraction analysis) from concept 2 in Fig. 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. 8. A difference between the RODOS and the Twincer® exists only for the finest particles (<1.5 µm), which cannot be dispersed completely into primary entities by the Twincer®. In contrast, the Twincer® 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) may be necessary to fill large powder weights in the dose compartments of the Twincer® having a fixed volume. In spite of a 12.5 times lower dispersion pressure for the Twincer® (4 kPa, which equals 0.04 bar) compared to the RODOS disperser (0.5 bar), the Twincer® de-agglomerates such a powder cake more effectively.

**Conclusions**

Although the machined copies of the Twincer® used for this *in vitro* study with colistimethate sodium were not fully optimised yet with respect to air flow resistance, powder entrainment from the dose system, inhaler accumulations and discharge flow from the mouthpiece, it has
been shown that high fine particle fractions can be obtained as the result of a high de-agglomeration efficiency. Special particle engineering processes to reduce the interparticulate forces are not necessary. A 2 mg dose of budesonide can be dispersed at 1 kPa with the Twincer® with the same efficiency as a 0.2 mg dose at 4 kPa with the Turbuhaler®. 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 μm) appears to be effective in reducing this accumulation inside the classifiers to less than 5% of the total dose at all flow rates. The remaining inhaler losses are found in the discharge channels but by directing bypass flows around the discharge holes, these losses can be further reduced to a total inhaler accumulation of only 5–6% (for colistimethate sodium) at 4 kPa. The Twincer® 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.

With the current Twincer® design, powder doses up to 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 dose and the good moisture protection of the drug formulation in a blister make the Twincer® also suitable for other applications, like the administration of rhDNAse in CF. Its simple design reduces the production costs of the Twincer®, 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. 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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