Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 260 (2003) 187–200
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Air classifier technology (ACT) in dry powder inhalation Part 1. Introduction of a novel force distribution concept (FDC) explaining the performance of a basic air classifier on adhesive mixtures

A.H. de Boer [a,*], P. Hagedoorn [a], D. Gjaltema [a], J. Goede [b], H.W. Frijlink [a]

[a] *Groningen University Institute for Drug Exploration (GUIDE), Department of Pharmaceutical Technology and Biopharmacy, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands*
[b] *Sofotec GmbH & Co, KG, Weismüllerstrasse 45, 60314 Frankfurt, Germany*

Received 11 December 2002; received in revised form 1 April 2003; accepted 13 April 2003

Abstract

Air classifier technology (ACT) is introduced as part of formulation integrated dry powder inhaler development (FIDPI) to optimise the de-agglomeration of inhalation powders. Carrier retention and de-agglomeration results obtained with a basic classifier concept are discussed. The theoretical cut-off diameter for lactose of the classifier used, is between 35 and 15 μm for flow rates ranging from 20 to 70 l/min. Carrier retention of narrow size fractions is higher than 80% for flow rates between 30 and 60 l/min, inhalation times up to 6 s and classifier payloads between 0 and 30 mg. The de-agglomeration efficiency for adhesive mixtures, derived from carrier residue (CR) measurement, increases both with increasing flow rate and inhalation time. At 30 l/min, 60% fine particle detachment can be obtained within 3 s circulation time, whereas at 60 l/min only 0.5 s is necessary to release more than 70%. More detailed information of the change of detachment rate within the first 0.5 s of inhalation is obtained from laser diffraction analysis (LDA) of the aerosol cloud. The experimental results can be explained with a novel force distribution concept (FDC) which is introduced to better understand the complex effects of mixing and inhalation parameters on the size distributions of adhesion and removal forces and their relevance to the de-agglomeration in the classifier.

Keywords: Dry powder inhalation; Air classifier technology; Adhesive mixtures; Powder dispersion; Force distribution concept; Carrier retention

1. Introduction

The performance of a breath controlled dry powder inhaler (DPI) depends on the properties of the powder formulation, the design of the device and the inspiratory manoeuvre by the patient. All three aspects have been subject of detailed investigation in the past decades. Many approaches have been presented to optimise powder formulations for inhalation in respect of dose consistency and obtained fine particle fraction (FPF) during inhalation. Various size fractions, of mostly alpha lactose monohydrate, have been proposed as most favourable filler or carrier excipient (e.g. Bell et al., 1971; Timsina et al., 1994). Several studies are known in which the positive effect from the presence of very fine lactose in carrier-based

* Corresponding author. Tel.: +31-50-3633286; fax: +31-50-3632500.
E-mail address: a.h.de.boer@farm.rug.nl (A.H. de Boer).

0378-5173/03/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00250-3

formulations on the fine particle dose is described (e.g. Arnold et al., 1993; Srichana et al., 1998; Zeng et al., 1998, 2000a). Others reported the complex effects of lactose grade (Larhrib et al., 1999) and carrier surface properties (Kawashima et al., 1998; Podczeck, 1998a, 1999; Zeng et al., 2000b) on the interaction forces between drug and carrier particles. It has been recommended to use carrier particles with a very specific surface rugosity (Ganderton and Kassem, 1991; Podczeck, 1998b), to treat the carrier surface mildly in a (ball) milling process (Staniforth, 1995) or to co-process carrier particles with so-called force control agents (Begat et al., 2001).

It is quite evident that the degree of powder de-agglomeration during inhalation is proportional to the energy input for dispersion, which for breath controlled DPI's depends on the inspiratory flow rate. Many different powder de-agglomeration principles have been patented, of which only a few have reached the market. They have to transfer the kinetic energy of the inspiratory flow rate into removal forces that separate the drug and carrier particles from each other. To avoid dependence of the inspiratory flow manoeuvre, application of electromechanical energy has been proposed (Han et al., 2002). From the viewpoint of efficacy in utilising the available breath energy, most favourable are principles that are designed to sustain the exertion of mechanical disruption forces on the powder during inhalation, e.g. by establishing a certain residence time for the powder inside the dispersion principle (Herold et al., 1994). It is quite disappointing that most studies on the improvement of inhalation powders and device developments were performed separately so far. It is obvious that neither development alone provides optimal performance for the combination. Only optimisation between the drug formulation and inhaler design can yield a maximal fine particle dose. We developed air classifier technology (ACT) in order to maximise powder de-agglomeration during inhalation. Specifically for different classifier concepts, we optimised adhesive mixtures that yield high FPFs without having to add special agents or to use sophisticated and expensive drug particle engineering techniques to control the adhesive forces between the drug and carrier particles. Furthermore, we developed a force distribution concept (FDC) to explain the behaviour of adhesive mixtures in an air classifier during inhalation, which is the result of complex and partly interacting effects that occur during powder mixing and inhalation. FDC also appears to be useful in controlling and balancing these effects. In this first part of a series of articles on ACT, the performance of a basic classifier concept with carrier retention is discussed and explained with the FDC.

2. Theory

2.1. Particle interaction and separation forces

The relevant types of interaction forces and possible modes of adherence between the (drug and carrier) particles in adhesive mixtures for inhalation have been summarised and discussed by various authors (e.g. Hinds, 1982; Hickey et al., 1994; Podczeck, 1996). Most likely to occur during mixing of dry powders are van der Waals and Coulombic forces. Although the likely type and mode of interaction force may be known; the orders of magnitude for these forces between dissimilar particles of known chemical compositions (drug and carrier) are often uncertain. They vary with size, shape, rugosity and hardness of the adhering particle, as well as with surface roughness and contamination of the carrier particle, the intensity (and duration) of the press-on forces during mixing and the relative humidity. If the scale of the rugosity of the carrier particle exceeds certain values, multiple contact points and interlocking are possible. Considering the difference in size between micronised drug and carrier particles in adhesive mixtures for inhalation, the type of adhesion between such particles is basically that between a sphere and a flat surface. The size of adhesive forces for this situation is proportional to the diameter (d) of the drug particle for all types of relevant interaction forces (Table 1). Podczeck (1996) experimentally found with centrifuge experiments that the median adhesion force increases with the press-on force while the press-on force is still low, but reaches a more or less constant value at press-on forces above approximately 10^{-11} N.

Separation forces for particles adhering to the surface of a carrier particle, which can be derived directly from the kinetic energy of the inspiratory airstream, are drag and lift forces, shear and friction forces and inertial forces (Table 1). For micronised particles attached to a carrier crystal, drag and lift forces are not

Table 1
Review of relevant interaction and separation forces for adhesive mixtures in dry powder inhalation

Interaction force	Proportionality	Separation force	Proportionality
van der Waals	$F_I \propto d \times x^{-2}$	Drag and lift	$F_S \propto d$ (or d^2)
Coulombic	$F_I \propto q^2 \times x^{-2}$ ($q \propto d^{0.5}$)*	Shear and friction	$F_S \propto D^3$
Capillary	$F_I \propto \gamma \times d$	Inertial	$F_S \propto \rho \times d^3$

d: drug particle diameter, x: separation distance between drug particle and carrier surface, q: amount of particle charge; (*) correlation between q and d is for particles >0.1 μm, γ: surface tension of the liquid between the particle and the surface, ρ: drug particle density, D: carrier diameter.

the most effective type of removal forces. They are widely proportional to the first power of the particle diameter and act only when there exists a velocity difference between the air and the particle. Fine particles can find shelter from drag and lift forces when the carrier surface exhibits a rugosity on a scale being larger than the diameter of the drug particle (e.g. for granular or coalescent carrier structures). Inertial forces are the most effective type of separation force for drug attached to carrier particles. They include vibration, centrifugal and collision forces. In contrast with drag, lift and friction forces, inertial separation forces yield potentially a favourable combination with high carrier rugosity. A rough structure does not basically influence the efficacy of inertial separation forces but it provides detached drug particles a free path to travel away from the carrier particle on the side of collision. Large pores may also host larger drug agglomerates. If the drug-to-drug interactions (cohesion forces) in such an agglomerate are stronger than the adhesion forces between drug and carrier particles, the agglomerate may be released as a whole. This requires much lower (collision) velocity than detachment of a single particle, because of the much higher inertia for the agglomerate. If, on the other hand, the adhesion forces are stronger, the drug-to-drug interaction is the weakest link and the number of detached particles on impact will increase with increasing number of drug-to-drug interactions (increasing carrier payload).

2.2. Air classifier technology

Most inhalers discharge the dose within a very short time period. The powder rapidly passes the de-agglomeration zone inside the inhaler and only a minor fraction of the available energy offered by the inspiratory airflow is utilised for disintegration. We chose ACT for powder de-agglomeration, because it fulfils all necessary requirements for maximal fine particle detachment. An air classifier is meant to classify particles upon size. In its most basic design, such a classifier is a cylindrical chamber with a tangential air supply channel and a discharge channel starting from the centre of one of its circular ends. If designed correctly, the larger carrier particles in such a classifier can be retained and only detached drug particles are discharged with the inspiratory airstream. The classification is the result of the counter acting of two forces (Fig. 1): the drag force (F_D) and the centrifugal force (F_C). The drag force (Stokes) is proportional to the first power of the particle diameter and dominates for fine particles. Consequently, such particles are entrained by the air into the discharge channel of the classifier. The centrifugal force is proportional to the third power of the diameter and strongest for the larger particles that are retained. The exact cut-off diameter depends on the design and dimensions of the classifier chamber, the air velocity inside this chamber and particle shape and density. Practically, the cut-off efficiency curve is not a step-function. Similarly as for an inertial impactor, a minor passage of particles with diameters that are larger than the theoretical

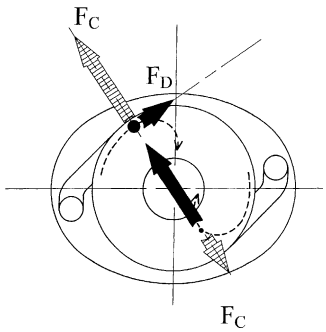

Fig. 1. Schematic presentation of the forces acting on the particles during circulation in a basic air classifier with cylindrical chamber.

cut-off diameter occurs for reasons that are given in the discussion of the results.

Carrier retention has many advantages. Carrier circulation within the classifier chamber is continued for the whole duration of inhalation. This guarantees maximal utilisation of the available energy for de-agglomeration. The break-up forces that are generated during circulation are a mix of centrifugal, collision and friction forces. For a basic classifier with a cylindrical circulation chamber as shown in Fig. 1 (top view), carrier particle collisions with the inner walls of the chamber occur particularly at the positions where the inner wall is interrupted by the air supply channels. These collision and centrifugal forces are responsible for the detachment of both primary and agglomerated drug particles. Friction forces, from sliding of particles and agglomerates along the cylindrical wall, further disrupt drug agglomerates into smaller entities (second step in the two-step de-agglomeration). Drug particles adhering to the inner wall as a result of contact with the powder are wiped off again by the coarser carrier particles (sweeper action). For investigative purposes, retained carrier particles can be analysed upon residual drug after inhalation, which provides valuable additional information to the FPFs collected in inertial impactors. This residual drug attached to the carrier particles that have been retained in the classifier during inhalation, is referred to as 'carrier residue' (CR). For a better comparison between different experiments, corrections for a minor carrier passage (release from the classifier chamber) are made by extrapolating CR to 100% retainment. Retention of carrier particles (from adhesive mixtures) and larger drug agglomerates (from spherical pellet formulations) also prevents that these particles are deposited in the throat. This eliminates the occurrence of local side effects. Air classifiers can also be designed to discharge carrier particles with a controlled rate, as will be discussed in subsequent parts of this series of papers. This has the advantage that retained carrier crystals do not have to be removed from the inhaler in between inhalations.

2.3. Force distribution concept

The fine drug particle fraction obtained during inhalation from a DPI is the result of a competition between the interaction forces within the powder and the separation forces derived from the inspiratory airflow through the inhaler. Because of the proportionalities between these forces and the drug particle diameter (Table 1), the size distributions of both forces depend on the size distribution of the drug. Micronised solid drugs for inhalation exhibit narrow size distributions, which are mostly within the range between approximately 0.5 and 7.5 μm, depending upon the type of drug (site of action). A further contribution to the polydisperse nature of the interaction forces is obtained from the variety of particle interactions and carrier bonding sites. According to Staniforth (1987), both cohesive and adhesive forces may be expected in a mixture with fine and coarse particles. Podczeck (1996) investigated adhesion and autoadhesion (cohesion) for salmeterol and lactose and concluded that the adhesion between drug and excipient is clearly with higher force than the cohesion between either drug or carrier particles. Carrier bonding sites include areas with a high degree of surface impurities and/or irregularities. Adhering fines and carrier surface discontinuities are places where multiple contact points may exist. Adhering impurities and lactose from the mother liquor may provide sites with higher bonding energy. Such sites could also be susceptible to plastic deformation so as to increase the contact area between drug and carrier particles. Moreover, they are the sites with potentially the highest degree of water adsorption (by peptides and water soluble proteins), which may result in capillary forces between the drug and carrier particles. Finally, the mixing process may have great influence on the drug-to-carrier interactions.

The separation forces generated in an air classifier exhibit a certain size distribution too. The centrifugal force (F_C) is proportional to the drug particle mass ($m \propto d^3$) and the square of the tangential particle velocity (U): $F_C = m \times U^2/R$ (where R is the diameter of the classifier chamber). The impaction force (F_I) exerted on a drug particle attached to a colliding carrier crystal is proportional to the rate of change in carrier particle velocity ($a = dU/dt$) and the drug particle mass: $F_I = m \times a$. If the separation force has a component of sufficient quantity acting in the correct direction, adhesion forces are overcome, and the drug particle is released. It has been shown (Dickhoff et al., 2002) that a slight increase in mean drug particle diameter may already cause a substantial increase of the percent of drug detached from the carrier

particles. This is in spite of an expected increase in the adhesive forces (Table 1).

All these variables influencing the adhesive and separation forces, make it difficult to investigate or predict the net effect of a change in material characteristics or conditions during mixing and inhalation, particularly because interactions between these variables and so-called correlated effects exist. For example, an increase in the obtained FPF during inhalation can be obtained by decreasing the carrier surface rugosity. To achieve this goal, the use of a finer carrier size fraction is often recommended or lactose fines can be added to the mixture. However, a change in size distribution changes the carrier bulk properties during mixing too. It furthermore changes the carrier payload (amount of drug particles per unit carrier surface area) and the acceleration (after collision) of carrier particles in the classifier, thus affecting the average tangential particle velocity in the classifier. So, what is believed to be an improvement from reducing the carrier surface rugosity, might as well be an effect from changing the carrier bulk properties or carrier payload. The net result of all these changes is difficult to predict since their respective orders of magnitude are not known. For this reason, we developed our FDC. FDC shows the possible effects of various variables during mixing and inhalation in terms of size distributions for the interaction and separation forces. FDC also allows us to explain and predict these effects by anticipating how the force distribution curves will change by changing certain variables. The concept is primarily based upon comparative presentation of both force distribution curves, but includes drug detachment rate studies as well, as will be discussed in this paper and in following parts of our series of articles on ATC.

As a first step in the application of FDC for a basic classifier, an assessment of the size distributions of the forces is made on the basis of the size distribution of the drug, which is obtained from dry laser diffraction analysis (LDA), using the cumulative volume undersize curve as function of the particle diameter. Arithmetic mean diameters are computed for selected size classes and calculations for the centrifugal force ($F_C = m \times U^2/R$) per size class are made for the average tangential air velocity U inside the classifier, which is derived from the inspiratory flow rate through the classifier chamber and its dimensions. This yields quite realistic values for F_C, providing that all carrier

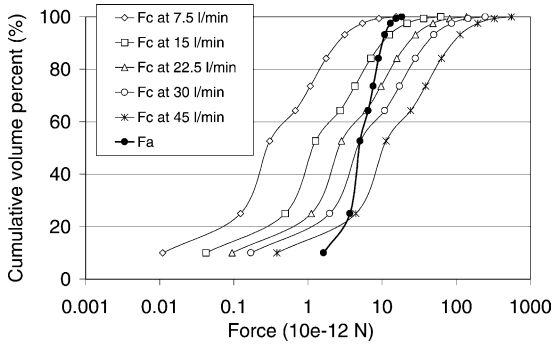

Fig. 2. Presentation of the force distribution concept (FDC): comparison of the size distributions of centrifugal separation forces in the classifier at five different flow rates and that of the adhesive forces in the mixture. See text.

particles travel with air velocity, all drug particles have the same density and are detached as single entities. As a result of the computations made, the centrifugal forces correlate with volume fractions in a comparable way as the particle diameters. Thus, they can be presented in a cumulative volume undersize curve as function of F_C. This is relevant to the application of FDC, as will become clear. The results of such calculations for F_C are shown in Fig. 2 for five different flow rates. Similarly, adhesive forces (F_A) can be calculated, for instance assuming that they are van der Waals forces and that the proportionality constant between the drug particle diameter and the adhesive force is the same for all particles. Expressed in the same way as the removal forces (cumulative volume percent as function of F_A), the span of the range for these adhesive forces ($F_A \propto d^1$) is theoretically much smaller than that for the separation forces, which are proportional to the third power of the diameter (Fig. 2). Because of the varieties in bonding sites and exerted press-on forces during mixing, the numerical values of the adhesive forces are less realistic than those for the centrifugal forces. Besides, the simplified calculation does not take account of the possible adherence of small drug agglomerates (next to primary particles) to carrier crystals, nor of differences between air and carrier particle velocities inside the classifier chamber (relevant to the calculation of F_C). However, computation of the precise numerical values for the forces is not intended. FDC has been developed to explain particularly the changes in the force distribution curves as the result of changing the conditions during mixing and inhalation. Therefore,

considering the size distributions of these forces in relation to each other between two different situations is the primary objective. For this, absolute values are not necessary. Investigating the relative influence of both forces relies on CR measurements (described in Section 2.2), which are part of FDC.

The CR is a measure for the coordinates of the intersection of both force distribution curves. If the separation forces are relatively small compared to the adhesive forces (as in Fig. 2 for F_C at 7.5 l/min), the *Y*-coordinate of the intersection will correspond with a high cumulative volume percent, indicating that CR is nearly 100%. With increasing flow rate, the size distribution of the separation forces shifts to higher values, which decreases the *Y*-coordinate of the intersection with the curve for the adhesive forces. For example in Fig. 2, the cumulative volume percent of the drug for which adhesive forces were not exceeded by separation forces at 45 l/min is only 22%. Consequently, CR at 45 l/min will be much lower than that at 7.5 l/min. By varying the flow rate for the same mixture between two extremes, only the position of the size distribution curve for the separation forces relative to the *X*-axis is changed, whereas its shape remains the same. Changes in the shape and position of the distribution curve for the adhesive forces are primarily the result of changes in the circumstances during mixing. Such changes may also influence the shape of the curve for the separation forces, e.g. by agglomeration of drug particles (increased drug particle inertia). Changes in the shape of the curves will also result in a shift of the *Y*-coordinate for the intersection of the curves. So, a change in CR between two different (mixing or inhalation) situations may be explained in terms of changes in position and shape of the force distribution curves, which is helpful for explaining the obtained effects in these situations. Some practical applications of FDC will be discussed more in detail in this, and next parts of our series of air classifier articles.

The *Y*-coordinate of the intersection is only a measure for the CR. This confines comparison of the force distribution curves to mixtures tested under the same inhalation conditions with respect to type of inhaler and inhalation time. An increase in inhalation time will result in a widening of the range of separation forces, because more extremes (on both sides) are generated. Although this does not necessarily change the position of the intersection of both force distribution curves dramatically, an increase in inhalation time is known to decrease the carrier residue. For this, many possible explanations exist. A separation force of sufficient size has to act in the correct direction before a drug particle can be detached from the carrier surface. It may be expected that several carrier particle collisions are necessary before the precise conditions are met. It may also be expected that repeated action (in different directions) of separation forces of lower size than initially necessary for detachment weaken the adhesive force, as a result of which detachment becomes more easy. Both conditions require a certain circulation time for the powder inside the classifier and make the proportionality between the intersection and the CR dependent of the inhalation time.

3. Materials and methods

3.1. Test inhalers with a basic air classifier

A home constructed test inhaler with a basic air classifier concept is shown in Fig. 3. The classifier exists of a metal cylindrical housing with a height to diameter ratio <1. The basic concept has two air supply channels that end as a tangent to the cylindrical wall in order to create a tangential airflow inside this chamber. One of the air channels also serves as powder channel. The classifier chamber is constructed of stainless steel and has for the test inhaler used in this study an inner diameter of 22 mm. During inhalation experiments the classifier is connected to the earth to avoid electrostatic charging. In the centre of the circular top plate is a discharge channel with slightly increasing inner diameter towards its exit, having the same longitudinal axis as the classifier chamber. The channel protrudes partly through the top plate into the classifier chamber to improve carrier retention. Around the discharge channel is a tapered mouthpiece. The annular chamber in between the discharge channel and mouthpiece cylinder is a passageway for sheath flow with which (a) the inhaler resistance can be controlled and (b) drug deposition in the mouth can be reduced. The classifier of the test inhaler has a rounding between the circular bottom and the cylindrical wall. The inhaler shown in Fig. 3 has no integrated dose (measuring) system. Doses have to be inserted manually or be dispensed from a separate dose measuring principle that can be

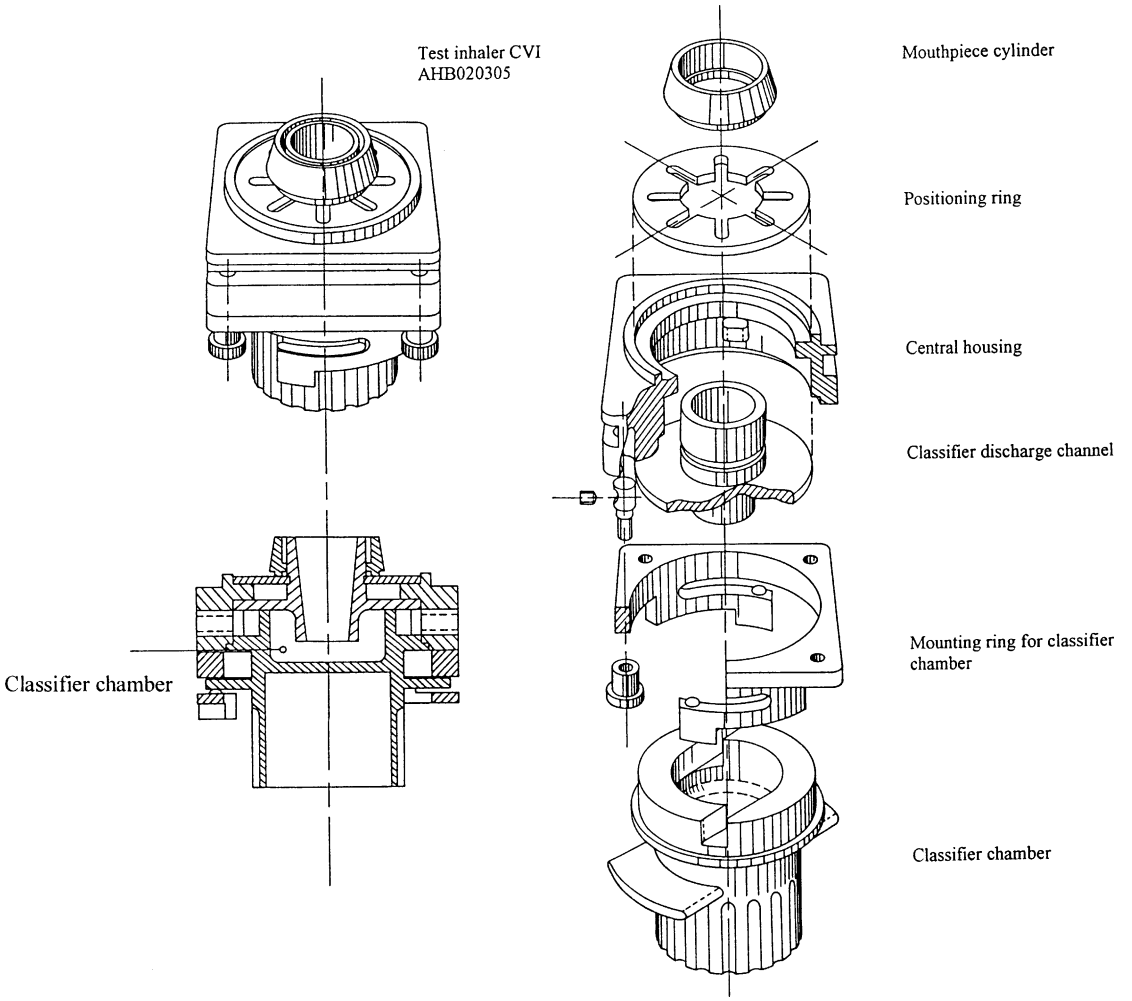

Fig. 3. Presentation of a test inhaler with a basic air classifier concept.

connected to the test inhaler. Retained carrier particles can be collected for analysis by disassembling the classifier chamber. Our ACT already finds application in many different (both marketed and test) inhalers. Their development involved testing of many different drug formulations. The essence of this article is to explain only the general performance and specifications of the basic classifier, for which we made use of results from these studies. This has the consequence that some figures shown in this manuscript (e.g. Figs. 5 and 6) represent many different formulations and size fractions of lactose. The experiments were selected, however, such that they are either comparable or to be considered as duplicate experiments.

3.2. Materials and special carrier size fractions

The drug used for experimental determination of the cut-off diameter of the basic classifier was colistin sulphate (Duchefa Farma, The Netherlands). Double micronisation of the drug, by subsequent jet milling (GfM, Germany) and ball milling (in a ceramic container on a home constructed drive), yielded a favourable size distribution for cut-off experiments, ranging from <1 to 87 μm with a median value of 2.14 μm (from laser diffraction characterisation). Budesonide for the CR experiments was supplied as a free sample by Asta Pharma (Germany) in a size distribution with 10% <0.54 μm and 100% <4.60 μm

(X_{50} = 1.04 μm) as measured with LDA (HELOS Compact KA with RODOS disperser, Sympatec, Germany). The budesonide was screened through a 90 μm sieve to break-up (and remove) hard agglomerates before making mixtures. Carrier materials were Capsulac 60 (Meggle, Germany), Pharmatose in different grades (DMV International, The Netherlands) and special carrier size fractions prepared from Pharmatose. All size fractions had a relative width (ratio of the span of the size range to the mean fraction diameter) between 0.25 and 0.4. The fractions were prepared in small batches of approximately 100 g by subsequently 20 min vibratory sieving (Analysette 3, Fritsch, Germany) and 20 min air jet sieving (A200, Alpine, Germany). All fractions have been checked upon size distribution and residual amount of fines with LDA.

3.3. Adhesive mixture preparation and characterisation

Adhesive mixtures of budesonide with different lactose carrier materials were prepared in a batch size of 25 g, using a stainless steel container (160 ml) in a Turbula T2C (Willy A. Bachofen AG, Switzerland) tumbling mixer at 90 rpm. Mixing time was 10 min. Mixture homogeneity was tested by taking 10 random samples (of 20–25 mg) from each mixture. The samples were dissolved in 15–20 ml of 100% ethanol and the drug solution was cleared from lactose crystals using a centrifuge (5 min at 3000 rpm; Rotana 3500, Hettich, Germany) and diluted (if necessary) before measuring the drug concentration spectrophotometrically at 242.8 nm (PU 8720 UV-Vis, Philips, The Netherlands).

3.4. Carrier cut-off and retention efficiency experiments

For the carrier cut-off experiments, colistin sulphate was mixed with a small amount (16.7% by weight) of a special lactose size fraction (150–200 μm, derived from Pharmatose 100 M) acting as a sweeper for fine drug particles adhering to the inner classifier walls. Individual doses of 25 mg of this mixture were inserted into the powder channel to the classifier chamber before the solenoid valve (with timer) was opened for a period of 3 s to start a flow through the test inhaler. Six doses were inserted at each flow rate while test inhaler was connected to a special inhaler adapter (INHALER^{TM} 2000, Sympatec, Germany) for LDA of the emitted aerosol cloud (de Boer et al., 2002a,b). The experimental cut-off diameter equals the X_{100}-value of the emitted aerosol.

Carrier retention efficiency data, presented as function of the flow rate (Fig. 5A at 30 and 60 l/min) have been derived from different studies, all of them with different size fractions of Pharmatose and budesonide concentrations between 0.4 and 1% (as explained in Section 3.1). For the percent carrier passage (equals 100 minus percent retention) as function of inhalation time (Fig. 5B), mixtures with 0.4% budesonide and two different carrier size fractions (45–63 and 150–200 μm, prepared from Pharmatose 150 M) were used. For Fig. 5C (the effect of dose weight on percent carrier passage), different amounts of Pharmatose 325 M (without drug) were added to the classifier chamber. Each datapoint in Fig. 5A and B (from cascade impactor experiments) is the mean of two series of 10 inhalations each; in Fig. 5C, each datapoint represents a single inhalation experiment.

3.5. Cascade impactor analysis (CIA) and carrier residue measurements

A glass constructed four stage cascade impactor of the Fisons type (MSLI of the type described by Hallworth and Andrews, 1976) was used for measuring the FPF, which for this study is defined as the sum of the fractions deposited on the stages 3 and 4, expressed as percent of the real dose. The impactor has geometrical cut-off diameters for the second stage of 12.35 μm at 30 l/min, respectively 8.74 μm at 60 l/min for lactose (density is 1.54 g/cm^3). The impactor was operated in combination with a dry bent inlet tube with large radius (to avoid de-agglomeration of powder within this port by particle collision with its inner wall) and a timer controlled solenoid valve to start and stop the flow through the test inhaler. Each cascade impactor value (Fig. 6) is the mean of two series of 10 inhalations. For the CR measurements, of which the results are presented in the Figs. 7 and 8, the test inhaler was connected to a small wash bottle (single shot impinger) to reduce the volume between the test inhaler and the solenoid valve. After each inhalation, the retained carrier was removed from the test inhaler and treated similarly to the mixture samples taken for

homogeneity testing in order to analyse the residual amount of drug (CR). In all our experiments, CR is expressed as percent of the original carrier payload and corrected for a minor carrier discharge from the classifier (passage) during inhalation by linear extrapolation to 100% retention. The CR values presented in Fig. 7 are the mean of three inhalations; those in Fig. 8 have been averaged for two series of five inhalations each.

3.6. Laser diffraction experiments

For LDA of the aerosol cloud from the test inhalers, the special inhaler adapter was used as referred to in Section 3.4. For determination of the cut-off diameters and the size distributions of the drugs and carrier materials, a Sympatec Compact/KA with standard HELOS software (for Fraunhofer calculation; Sympatec Germany) was applied in combination with a prototype inhaler adapter (University of Groningen) and a 100 or 200 mm lens (depending on the size distribution to be measured). Drugs and carrier materials were fed to the laser beam with a Sympatec RODOS dry powder disperser, operated at 3–5 bar. For measurement of the optical concentration in the aerosol cloud as function of the inhalation time (Figs. 9 and 10), a Sympatec HELOS/BF-MAGIC (with 100 mm lens) was applied in combination with a Sympatec INHALER^{TM} adapter. Ten inhalations at 60 l/min were performed with a mixture of 4% budesonide and carrier size fraction 150–200 μm (from Pharmatose 150 M). Start of the measurements was synchronised (electronically) with opening of the solenoid valve; measurements were stopped after 3 s of inhalation. Because of increasing window pollution with increasing inhalation time, only the data from the first 2 s have been used. The area under the curve (AUC) for the mean value ($n = 10$) has been calculated for each time interval (0.02 s), being a measure for the amount of drug discharged from the classifier within this time interval. Next, the sum of the AUC values (end value) has been equated with the percent of dose emitted from the test inhaler (56.77%) as obtained from CR measurements under the same inspiratory conditions (60 l/min and an inhalation time of 2 s). Corrections for window pollution (of the laser diffraction adapter) have been made by increasing the base line between 0 and 0.5 s from 0 to 0.8%.

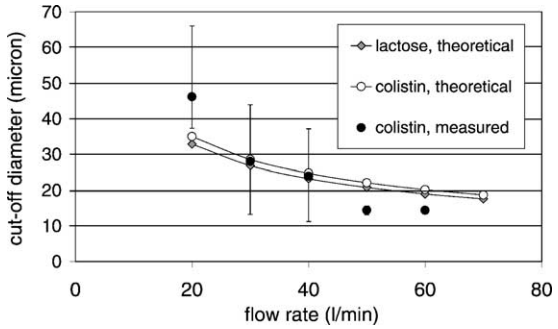

Fig. 4. Theoretical and experimental cut-off diameters of the basic air classifier as function of the inspiratory flow rate for colistin sulphate. The bars, in connection with the measured values, indicate the maximum and minimum values obtained.

4. Results and discussion

The airflow resistance of the basic classifier (0.051 kPa$^{0.5}$ min/l) is quite high without sheath flow. This corresponds with pressure drops of 2.3 kPa at 30 l/min, respectively 9.3 kPa at 60 l/min. Because we aim at a moderate air flow resistance (4 kPa corresponding with 60 l/min), approximately 50% sheath flow will be necessary for convenient operation of the test inhaler by a patient. Fig. 4 shows that the theoretical cut-off diameter of the basic classifier slightly decreases with increasing flow rate. The value between 35 and 15 μm for the range of flow rates between 20 and 70 l/min is high enough to guarantee complete emission of drug particles in the size range that is relevant to lung deposition, and low enough to expect effective retention of carrier size fractions with a lower class limit of 30 μm or higher. The experimental cut-off diameters (mean of six X_{100}-values from laser diffraction measurement of the emitted aerosol cloud) in this figure correspond fairly well with the theoretical values for colistin sulphate, although a certain discrepancy may be expected for a number of reasons. Most of all, the order of magnitude of various side effects cannot be estimated. The classifier chamber is relatively small and irregularly shaped particles bounce off at different angles after hitting the classifier wall. Some particles that are rebounced in the direction of the discharge channel may travel the short distance between the cylindrical classifier wall and this channel, before their orbit around this channel can be corrected by the tangential streamlines of the air. They may enter the

channel and be discharged (random passage of particles larger than the cut-off diameter). Also tribocharge may influence particle circulation within the classifier chamber. Finally, some particles may be released as small agglomerates, having a much lower (apparent) density than a solid particle of the same size. This gives a discrepancy between measured and calculated cut-off diameter for agglomerates, if the cut-off diameter is computed assuming that all particles are solid.

The carrier retention efficiency is presented in the Fig. 5A–C. Fig. 5A shows that retention depends on the flow rate. Nearly 100% retention for narrow carrier size fractions can be obtained (after 3 s inhalation time) when the mean fraction diameter is >300 μm at 60 l/min, respectively >150 μm at 30 l/min. The percent of retained carrier particles also depends on the inhalation time (Fig. 5B). Passage of particles larger than the theoretical cut-off diameter is a random occurrence, as has been explained in the discussion of Fig. 4. So, it may be expected that the number of events of a large particle entering the discharge channel increases with increasing circulation time inside the classifier chamber. The results are in agreement with Fig. 5A: the percent of carrier passage at the same flow rate and inhalation time, increases with decreasing mean carrier particle diameter. The number of particles circulating within the same volume increases with increasing classifier payload, and so does the number of particle–particle collisions per unit time. Therefore, it is not surprising that the percent of carrier particles emitted from the classifier increases with increasing dose weight (Fig. 5C). Acceptable retention values for the classifier in the presented test inhaler (>90%) require that the dose weight is below 20 mg.

Fig. 6 shows that FPF (as percent of real dose) collected from the cascade impactor does not show the expected correlation with the percent of drug released from the carrier crystals (expressed as 100 − CR). The data are for different adhesive mixtures with 0.4–1% budesonide and different carrier size fractions. For all mixtures, FPF is substantially lower than the corresponding percent of drug released from carrier, and a considerable spread in FPF at the same percent of detachment exists. There are different explanations for this discrepancy between the directly (100 − CR) and indirectly (FPF) measured fraction of drug detached from carrier. Losses of detached particles occur inside the inhaler (mouthpiece), the induction port to the impactor, connecting tubes between the impactor stages as well as from particles passing the final impactor stage. Some of these losses are the result of electrostatic effects which vary with circumstances

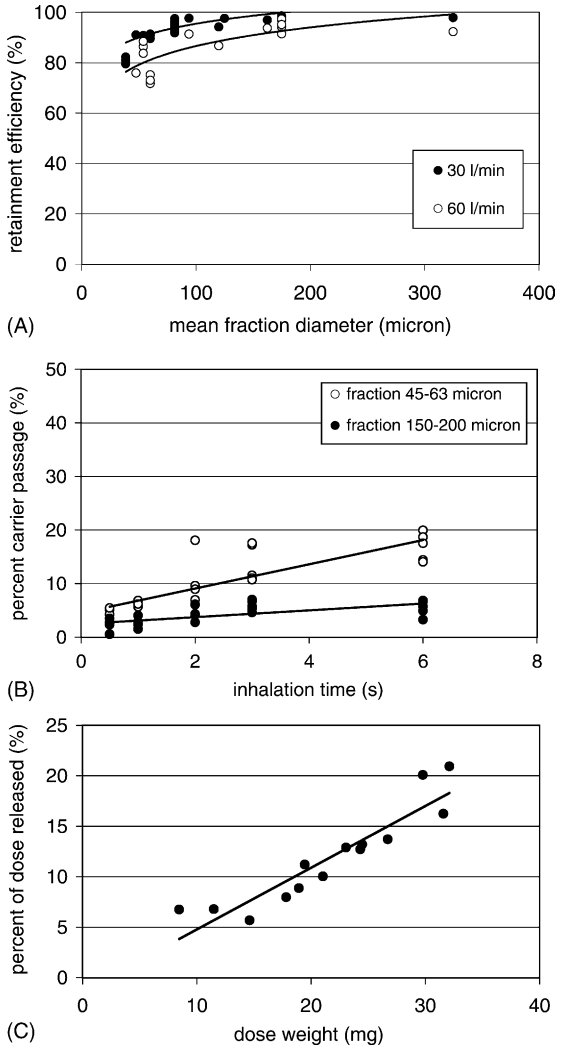

Fig. 5. (A) Carrier retention (withdrawal) efficiency (as percent of dose) in dependence of mean fraction diameter for size fractions from different types of Pharmatose at two different flow rates. Dose is 25 mg; inhalation time is 3 s. (B) Carrier passage (as percent of dose) from the test inhaler as function of the inhalation time for two size fractions derived from Pharmatose 150 M (45–63 μm) and Capsulac 60 (150–200 μm) at 60 l/min. Dose is 25 mg. (C) Carrier passage (as percent of dose weight) for Pharmatose 325 M at 30 l/min from the test inhaler as function of the classifier load (dose weight). Inhalation time is 3 s.

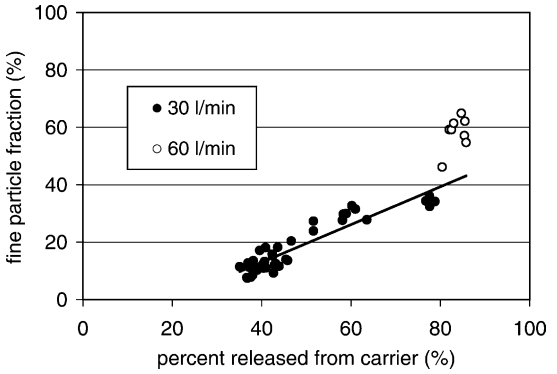

Fig. 6. Fine particle fraction (FPF) vs. carrier residue (CR) from the test inhaler both as percent of real dose, for different formulations (carrier size fractions) with 0.4–1% of budesonide at two different flow rates. Inhalation time is 3 s.

(e.g. relative humidity of the air, the number of preceding inhalations, cleaning procedures). They can only partly be controlled. Such losses contribute to the poor repeatability (within-laboratory variation) for cascade impactors in DPI-testing, as has been reported by Olsson et al. (1996) for the European Pharmacopoeia devices. The losses within the inhaler and induction port generally decrease with increasing flow rate. This may explain why the discrepancy between the percent of drug that has been detached from the carrier and the percent of drug that has been recovered as FPF is different for 30 and 60 l/min, as shown in Fig. 6. These losses are one of the reasons why we prefer to rely on percent CR values for formulation studies, explained with FDC, rather than on FPFs. There are two more important reasons for this preference. CR measurements are much less laborious and time consuming than cascade impactor experiments, whereas they yield reliable information based on single inhalations. Carrier particles discharged from a DPI collide with the inner wall of the induction port where they enter the sharp 90° bent. If the inhaler has a tangential discharge flow component (and most DPI's do so), collision also occurs by centrifugal action in the double tapered section of this induction port. These collisions contribute to powder de-agglomeration; the extent of the contribution being dependent on inhaler dispersion efficiency.

The discrepancy between FPF and percent of drug detached from carrier may have another important reason. Drug particles may not be released as single entities, but partly as agglomerates that are too large to reach the lower impactor stages for the FPF. This can be observed from a shift in deposition towards higher (1st and 2nd) impactor stages and particularly with LDA of the aerosol cloud (de Boer et al., 2002a,b). The effect occurs particularly at lower flow rates, when inertial separation forces are sufficiently high to detach such agglomerates (with much higher inertia than single particles) from the carrier crystals, but friction forces in the classifier are not yet high enough to disrupt them further into finer fragments. This aspect will be discussed more in detail in the next articles in this series on ACT.

Fig. 7 shows one of the possible ways to apply the FDC for the removal forces generated in a basic air classifier. For an adhesive mixture with 2% budesonide (on Capsulac 60 as carrier material), the percent CR decreases both with increasing flow rate and increasing inhalation time. As expected, the mean of the separation forces shifts to a higher value when the velocity inside the classifier chamber is increased. But also, a larger fraction of drug is detached when the circulation time is increased. Consequently, a reduction in flow rate from 60 to 30 l/min can be compensated to a significant extent by increasing the inhalation time from 0.5 to 3 s. The beams indicating the maximum and minimum values (of three inhalations) prove that the reproducibility of the measurement is quite high, particularly at the higher flow rate of 60 l/min. It can be concluded that the highest detachment rate is obtained within the first half second, which results in a release

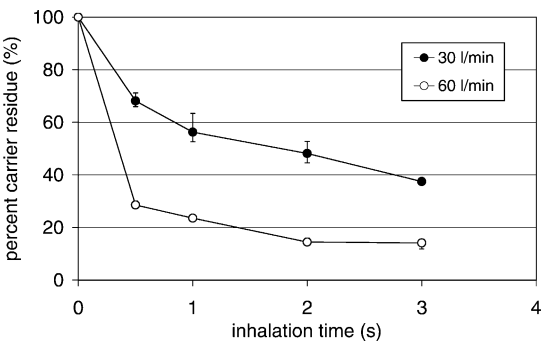

Fig. 7. Percent carrier redisue (CR), extrapolated to 100% retention, obtained with the test inhaler as function of flow rate (30 and 60 l/min) and circulation time for an adhesive mixture with 2% budesonide and Capsulac 60 as carrier. Dose is 10 mg ($n = 3$). The bars indicate the maximum and minimum values obtained.

of 51% of the 'end value' (after 3 s) at 30 l/min versus 83% at 60 l/min. Meaning thereby that longer inhalation times for this particular formulation are most relevant to fine particle detachment at the lower flow rate of 30 l/min. The data presented in Fig. 7 are important for classifier design and optimisation of the inhaler system, including the adhesive mixtures to be used in this inhaler regarding the desired carrier residence time (within the classifier), as will be discussed more in detail in next parts of this series of articles on ACT.

Fig. 8 compares the percent CR, percent detached (expressed as 100 − CR) and percent of dose emitted at 60 l/min for a formulation with 4% budesonide as function of inhalation time. The difference between emitted and detached fraction is the amount of drug accumulated in the inhaler's mouthpiece (IA), which is quite high for the test inhaler, as this device was designed primarily for CR measurements. Good knowledge of the detachment and dose emission rates (first derivatives of the curves in Fig. 8) are relevant to the design of classifiers with a controlled residence time for the carrier particles during inhalation and to understanding the underlying mechanisms for particle-to-particle interactions. The accuracy of emission rate measurement decreases with decreasing inhalation time. Not so much because shorter inhalation times cannot be controlled accurately, but rather because of fringe effects. The time necessary to establish a stationary flow through the inhaler, as well as the time during which a flow through the DPI is continued after the valve is closed in order to balance impactor and ambient pressure, gain relative importance with decreasing inhalation time. This depends on many factors, such as inhaler resistance, flow rate and impactor volume. In order to minimise these fringe effects, we minimised the volume of the flow diagram by using a wash bottle with small volume instead of a cascade impactor during CR experiments.

From an ongoing desire to further increase the sensitivity and accuracy of our experiments, the applicability of laser diffraction technique for emission rate measurements with the basic air classifier was investigated. Particularly the changes in drug detachment rate within the first 0.5 s of inhalation may be relevant to the application of FDC. Fig. 9 shows the optical concentration of the aerosol cloud from the test inhaler as function of the inhalation time for the same formulation as presented in Fig. 8. Being a real time measurement, fringe effects are excluded and the rate of change in optical concentration can be calculated for time intervals of 0.02 s (or shorter). By making suspensions (in saturated liquids) with increasing concentration of the same particle size fraction, it could be confirmed that there exists a proportional correlation between particle concentration of the suspension and optical concentration. This allowed computing of the optical concentration data into real particle concentration data. A quantitative presentation was obtained by equating the AUC for the time interval between 0 and 2 s with the emitted (percent of) dose after 2 s from CR

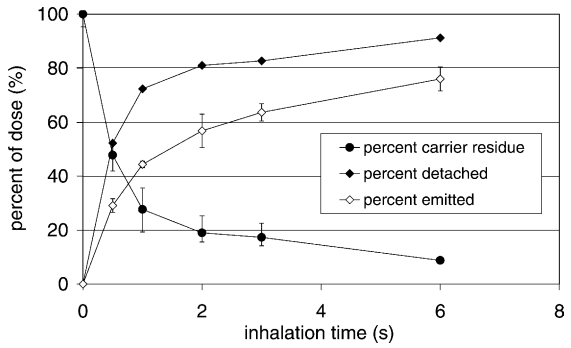

Fig. 8. Percent carrier residue (CR), percent drug detached (100 − CR) and percent emitted (100 − CR − IA) as function of inhalation time for a mixture with 4% budesonide and carrier size fraction 150–200 μm (from Pharmatose 150 M) obtained with the test inhaler at 60 l/min. IA is the percent of dose accumulated in the inhaler. The bars indicate the maximum and minimum values obtained.

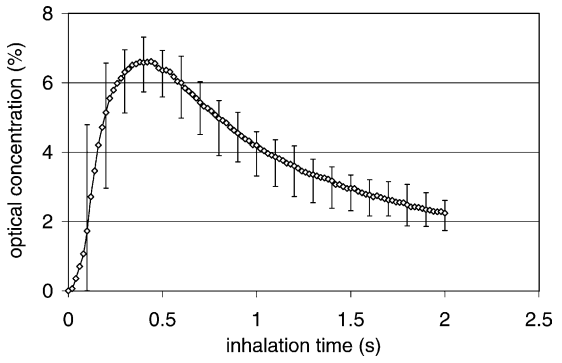

Fig. 9. Optical concentration of the aerosol cloud from the test inhaler as function of the inhalation time for the same mixture and the same inhalation conditions as presented in Fig. 8. The bars indicate the maximum and minimum values obtained.

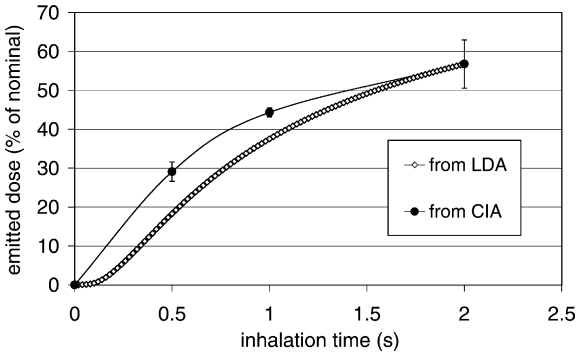

Fig. 10. Comparison of detachment rate obtained from two different techniques (LDA and CIA); data derived from Figs. 8 and 9. The bars indicate the maximum and minimum values obtained.

measurements (56.77% in Fig. 8). By calculating the AUC also separately for each of the time intervals (up to and including 2 s) and processing these values into a cumulative curve as percent of the end value (again 56.77% of the dose), an emission rate curve was obtained. This curve is shown in Fig. 10 in comparison with the emission rate curve from CR measurement. Confinement of the emission time to 2 s is for practical reasons; at longer times, necessary corrections for window pollution appeared to be too extreme.

Although both curves obtained from LDA and CR measurement show the same trend, they do not match completely. A perfect match could not be expected, however, as both techniques represent different series of inhalations. Finding a difference is also inherent in comparing the results obtained with different techniques. Finally, there is a difference in fringe effects, as discussed previously. The laser diffraction result seems somewhat more realistic for the first milliseconds of inhalation, because it requires some time before the particles are transported towards the classifier chamber and a steady circulation is achieved. On the other hand, the lag time shown by the LDA curve may be exaggerated, as detached drug particles need some time to travel to the laser beam too. It may not be surprising that the CIA results are somewhat higher, as the continuation of flow rate through the classifier after the valve has been closed generally takes more time than establishing a steady particle circulation after the valve has been opened.

In conclusion, air classifiers appear to be highly efficient in both the de-agglomeration of adhesive mixtures for inhalation and the separation of carrier and drug particles. Between 80 and 100% of the carrier dose can be retained in the classifier and more than 70% of the drug can be detached from the carrier crystals at a flow rate of 60 l/min within the first half second of inhalation, even for a non-optimised adhesive mixture. A decrease in flow rate can partly be compensated by an increase in inhalation time. The performance of a classifier can be explained with the statistical FDC presented in this paper. Analysis of retained carrier particles on residual drug is a fast and highly reproducible method for studying the drug detachment rate during inhalation, but more detailed information about the change in detachment rate within the first half second of inhalation is obtained from optical concentration measurement of the aerosol cloud with laser diffraction technique.

Acknowledgements

The authors wish to thank Sofotec (Frankfurt, Germany) for the cooperation in the air classifier development, DMV International (Veghel, The Netherlands) for the cooperation in lactose optimisation for adhesive mixtures, the Groningen University Workshop for constructing the various test inhalers and Mrs. J. Beekhuis for carefully screening the manuscript.

References

Arnold, K., Grass, P., Knecht, A., Roos, R., Sluke, G., Thieme, H., Wenzel, J., 1993. Inhalation powders and method of manufacturing them. European Patent No. 0663815 B1.

Begat, P., Green, M., Morton, D.A.V., Whittock, A., Staniforth, J., 2001. Powderhale^{TM}: a novel high-performance dry powder inhaler formulation technology for targeted and systemic drug delivery. Proc. Drug Delivery Lungs XII, 119–122.

Bell, J.H., Harley, P.S., Cox, J.S.G., 1971. Dry powder aerosols 1: a new powder inhalation device. J. Pharm. Sci. 10, 1559–1564.

de Boer, A.H., Hagedoorn, P., Gjaltema, D., Dickhoff, B.H.J., Frijlink, H.W., 2002a. Investigation of the relevant parameters for dispersion of adhesive mixtures in an air classifier during inhalation. Proc. Drug Delivery Lungs XIII, 7–10.

de Boer, A.H., Gjaltema, D., Hagedoorn, P., Schaller, M., Witt, W., Frijlink, H.W., 2002b. Design and application of a new modular adapter for laser diffraction characterization of inhalation aerosols. Int. J. Pharm. 249, 233–245.

Dickhoff, B.H.J., Ellison, M.J.H., de Boer, A.H., Frijlink, H.W., 2002. The effect of budesonide particle mass on drug particle

detachment from carrier crystals in adhesive mixtures during inhalation. Eur. J. Pharm. Biopharm. 54, 245–248.

Ganderton, D., Kassem, N.M., 1991. Aerosol carriers. International Publication Number WO 91/11179.

Hallworth, G.W., Andrews, U.G., 1976. Size analysis of suspension inhalation aerosols by inertial separation methods. J. Pharm. Pharmacol. 28, 898–907.

Han, R., Papadopoulos, G., Greenspan, B.J., 2002. Investigation of powder dispersion inside a SPIROS® dry powder inhaler using particle image velocimetry. Powder Technol. 125, 266–278.

Herold, H., Wollenschläger, A., Landen, H., Schmitt, F., 1994. Pulverinhalator. German Offenlegungsschrift DE 4239402 A1.

Hickey, A.J., Concesio, N.M., van Oort, M.M., Platz, R.M., 1994. Factors influencing the dispersion of dry powders as aerosols. Pharm. Technol. 58–64.

Hinds, W.C., 1982. Aerosol Technology. Wiley, New York, pp. 127–130; 284–288.

Kawashima, Y., Serigano, T., Hino, T., Yamamoto, H., Takeuchi, H., 1998. Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate. Int. J. Pharm. 172, 179–188.

Larhrib, H., Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 1999. The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. Int. J. Pharm. 191, 1–14.

Olsson, B., Aiache, J.M., Bull, H., Ganderton, D., Haywood, P., Meakin, B.J., Schorn, P.J., Wright, P., 1996. The use of inertial impactors to measure the fine particle dose generated by inhalers. Pharmeuropa 8, 291–298.

Podczeck, F., 1996. Assessment of the mode of adherence and the deformation characteristics of micronized particles adhering to various surfaces. Int. J. Pharm. 145, 65–76.

Podczeck, F., 1998a. The relationship between physical properties of lactose monohydrate and the aerodynamic behaviour of adhered drug particles. Int. J. Pharm. 160, 119–130.

Podczeck, F., 1998b. Adhesion forces in interactive powder mixtures of a micronized drug and carrier particles of various particle size distributions. J. Adhesion Sci. Technol. 12, 1323–1339.

Podczeck, F., 1999. The influence of particle size distribution and surface roughness of carrier particles on the in vitro properties of dry powder inhalations. Aerosol Sci. Technol. 31, 301–321.

Srichana, T., Martin, G.P., Marriott, C., 1998. On the relationship between drug and carrier deposition from dry powder inhalers in vitro. Int. J. Pharm. 167, 13–23.

Staniforth, J., 1987. Order out of chaos. J. Pharm. Pharmacol. 39, 329–334.

Staniforth, J., 1995. Improvements in and relating to carrier particles for use in dry powder inhalers. International Publication Number WO 95/11666.

Timsina, M.P., Martin, G.P., Marriott, C., Ganderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. Int. J. Pharm. 101, 1–13.

Zeng, X.M., Martin, G.P., Tee, S.-K., Marriott, C., 1998. The role of fine particle lactose on the dispersion and de-aggregation of salbutamol sulphate in an air stream in vitro. Int. J. Pharm. 176, 99–110.

Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 2000a. Lactose as a carrier in dry powder formulations: the influence of surface characteristics on drug delivery. J. Pharm. Sci. 90, 1424–1434.

Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 2000b. The influence of carrier morphology on drug delivery by dry powder inhalers. Int. J. Pharm. 200, 93–106.