Chapter 4

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

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Abstract

Air classifier technology (ACT) is introduced as part of formulation integrated dry powder inhaler development to optimise the dispersion of inhalation powders. Powder de-agglomeration and carrier retention results obtained with a basic classifier design are discussed in this chapter. The theoretical cut-off diameter for crystalline lactose of the classifier used for the experiments in this study is between 35 and 15 µm for flow rates ranging from 20 to 70 l/min. The carrier retention efficiency of narrow size fractions (of which the lower class diameters are larger than the cut-off value of the classifier) 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 degree of adhesive mixture de-agglomeration, derived from carrier residue measurements, 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% of the drug. More detailed information about the changes in detachment rate within the first 0.5 s of inhalation has been obtained from laser diffraction analysis of the aerosol cloud. The experimental results can be explained with a novel force distribution concept (FDC) which is introduced to obtain a better understanding of the complex effects of mixing and inhalation parameters on the size distributions of adhesion forces and removal forces (during inhalation) respectively.

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

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 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 drug and/or carrier particles with so-called force control agents (Begat et al., 2001). More recently, it has been proposed to reduce the carrier surface rugosity and impurities with special (re-)crystallisation and submersion techniques (e.g. Zeng et al., 2001a/b; Price et al., 2002; Iida et al., 2003).

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 (de Boer et al., 2004). 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 focussing on the improvement of inhalation powders and device developments were performed separately so far. It is obvious that neither development alone provides optimal performance of the combination, as successful drug detachment during inhalation is the result of careful balancing between the adhesive forces in the mixture and the separation forces that are generated during inhalation. Therefore, only optimisation between the drug formulation and inhaler design (formulation integrated dry powder inhaler development) 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 designs, we optimised different types of drug formulation which yield high fine particle fractions without adding special agents or using 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 performance 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. Adhesion and separation (detachment) 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. For the sake of simplicity all types of particle interaction forces in the powder mixture (including cohesive forces) are referred to as adhesive forces (F_A) in this manuscript. Although the types and modes of adhesive forces may be known; their orders of magnitude are often uncertain. They vary with the size, shape, rugosity and hardness of the adhering particle, as well as with the surface roughness and contamination of the carrier particle, the intensity (and duration) of the mixing process and the relative humidity. If the scale of the rugosity of the carrier particle exceeds certain values, multiple contact points and mechanical 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 the adhesive forces for this situation is proportional to the diameter (d) of the drug particle for all types of relevant interaction forces (Table 4.1).

Table 4.1. Review of relevant interaction and separation forces for adhesive mixtures in dry powder inhalation.

Type of interaction force	Proportionality	Type of separation force	Proportionality
Van der Waals Coulombic Capillary	$F_A \propto d.x^{-2}$ $F_A \propto q^2.x^{-2}$ $(q \propto d^{0.5})$* $F_A \propto \gamma.d$	Drag and lift Shear and friction Inertial	$F_R \propto d$ (or d^2) $F_R \propto D^3$ $F_R \propto \rho.d^3$
d = drug particle diameter x = separation distance between drug particle and carrier surface q = amount of particle charge (*the 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			

Detachment of drug particles from the surface of a carrier particle during inhalation can be achieved by transforming the kinetic energy of the air stream through the inhaler into drag and lift forces, shear and friction forces or inertial forces (Table 4.1). Of these forces, drag and lift forces are the least effective type of separation forces. They are widely proportional to the first power of the particle diameter (Stokes' Law) 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 has a rugosity on a scale being larger than the diameter of the drug particle however. This situation may be expected for granular and coalescent carrier structures, but also for large crystalline carrier particles with large surface discontinuities. Inertial forces are the most effective type of separation force for drug particles attached to carrier crystals. They include vibration (acceleration forces) as well as centrifugal and collision forces. In contrast with drag, lift and friction forces, inertial separation forces yield potentially a favourable combination with a high carrier rugosity. A rough structure does not basically influence the effectiveness 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. In addition, drug particles inside large carrier surface irregularities may find shelter from inertial and frictional press-on forces during the mixing process which increase the adhesive forces in the mixture. Large pores may even host larger drug agglomerates. If the drug-to-drug

interactions (cohesion forces) in such an agglomerate are stronger than the adhesion forces between the drug and carrier particles, the agglomerate may be released as a whole. This requires a 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 entire dose within a very short time period. The powder rapidly passes the de-agglomeration principle of the inhaler and only a minor fraction of the energy in the air flow through the inhaler is used for dispersion. We chose air classifier technology for powder de-agglomeration, because if fulfils all necessary requirements for maximal fine particle detachment. In a classifier, mainly inertial separation forces are generated and the larger carrier particles are kept in circulation for the duration of the inhalation manoeuvre, which enables to use the available energy for dispersion much more effectively.

An air classifier is meant to classify particles upon size. In its most basic design, it is a cylindrical chamber with a tangential air (and powder) supply channel and a discharge channel starting from the centre of one of its circular ends. The discharge channel has the same longitudinal axis as the cylindrical circulation chamber. If designed properly, the larger carrier particles in the classifier are retained and only detached drug particles are discharged with the inspiratory air stream. The classification is the result of the counter acting of two forces as shown in Fig. 4.1 for a classifier with two air inlet channels: the drag force (F_D) and the centrifugal force (F_C).

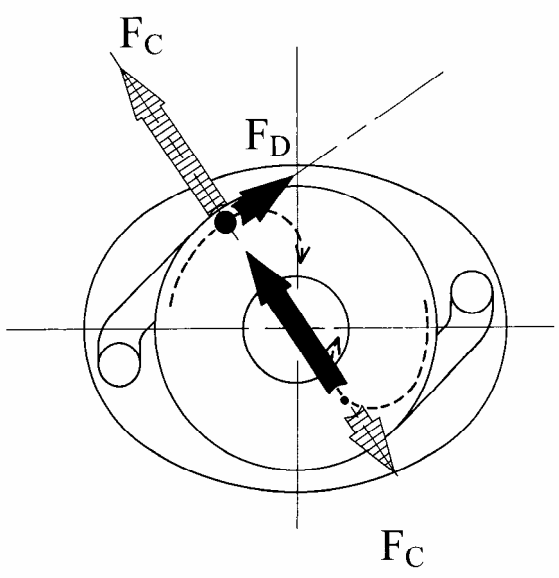

Figure 4.1. Schematic presentation of the forces acting on particles during circulation in a basic air classifier with cylindrical chamber. F_C is the centrifugal force and F_D the drag force.

The drag force (Stokes' Law) is proportional to the first power of the particle diameter and is dominant for fine particles. Consequently, fine particles are dragged by the air into the discharge channel of the classifier. The centrifugal force is proportional to the third power of

the diameter and highest for the larger particles, which are retained in the classifier. 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 curve is not a step-function. Similarly as for an inertial impactor, passage of some particles with diameters that are larger than the theoretical cut-off diameter occurs for reasons that will be given in the discussion of the results.

The separation forces that are generated in the classifier during inhalation are a mix of centrifugal, collision and friction forces. For a basic classifier with a cylindrical circulation chamber as shown in Fig. 4.1 (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 forces, and the centrifugal forces, are responsible for the detachment of both primary and agglomerated drug particles from the carrier crystals. Friction forces, from sliding of particles and agglomerates along the cylindrical wall, and collision forces further disrupt drug agglomerates into smaller entities (second step in the 2-step de-agglomeration process). Drug particles adhering to the inner classifier wall 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 fine particle fractions collected in inertial impactors. This residual drug still being 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 generally made by extrapolating CR to 100% retention. 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. The few carrier particles that do leave the classifier are deposited in the mouth (by centrifugal action) instead of in the throat. This reduces the occurrence of local and systemic side effects (as for instance hoarseness induced by cortico steroids). Air classifiers can also be designed to discharge carrier particles with a controlled rate, as will be discussed in the chapters 9 and 10. 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 dry powder inhaler is the result of a competition between the adhesive forces in the powder mixture and the separation forces during inhalation. Because of the proportionalities between these forces and the drug particle diameter (Table 4.1), the size distributions of both forces depend largely on the size distribution of the drug. Micronised solid drug particles for inhalation exhibit mostly size distributions in the range between 0.5 to 7.5 µm, depending on the type of drug (i.e. the precise site of action). A further contribution to the polydisperse nature of the adhesive forces is obtained from the great variety in particle interactions and carrier bonding sites. According to Staniforth (1986), both cohesive and adhesive forces may be expected in a mixture with fine and coarse particles. Podczeck (1996) investigated adhesion and auto adhesion (cohesion) for salmeterol and lactose and concluded that the adhesion forces between drug and excipient are clearly higher than the cohesion forces between either drug or carrier particles. Carrier surfaces (bonding sites) include smooth crystal planes as well as 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 crystallised on the carrier surface from residues of the mother liquor during the drying process may provide sites with higher bonding energy. Such sites could also be susceptible to plastic deformation (under the application of press-on forces during mixing), 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. All these special bonding places may be described with the term 'active sites'. Finally, the duration and the intensity of the mixing process may have a 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_T): $F_C = m.U_T^2/R$ (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: $F_i = m.a$. 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 in a classifier. This, in spite of an expected increase in the adhesive forces too (Table 4.1).

All these variables which influence 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 certain interactions between these variables exist and so-called correlated effects may occur. For example, an increase in the obtained fine particle fraction during inhalation can be obtained from 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 the 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, which affects the average tangential particle velocity in the classifier. Not to mention that the carrier retention efficiency decreases with decreasing mean carrier diameter (which reduces the effective carrier circulation time). Finally, the type of interaction may change from that between a sphere and a plate into a sphere-to-sphere adhesion when the carrier particles approach the size of the drug particles. This halves the adhesive force and also changes the mechanism and/or effectiveness of separation during inhalation. So, what is believed to be an improvement from reducing the carrier surface rugosity could as well be an effect from changing the carrier bulk properties, the carrier payload or the carrier circulation in the classifier. 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 a force distribution concept (FDC). FDC shows the possible effects of various variables during mixing and inhalation in terms of size distributions for the adhesion and separation forces. FDC also enables to explain and predict these effects by anticipating how the force distribution curves will change by changing certain variables. The concept is primarily based on comparative presentation of both force distribution curves, but includes drug detachment rate studies as well, as will be discussed in this and in next chapters.

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, using the cumulative volume undersize curve as function of the particle diameter. Arithmetic mean diameters are computed for selected size classes (within the entire size distribution) and calculations for the inertial separation force (e.g. $F_I = F_C = m.U_T^2/R$) per size class are made for the average tangential air velocity U_T 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_I, providing that al carrier 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 separation 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_I (instead of d). The results of such calculations for F_C are shown in Fig. 4.2 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 separation 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. 4.2).

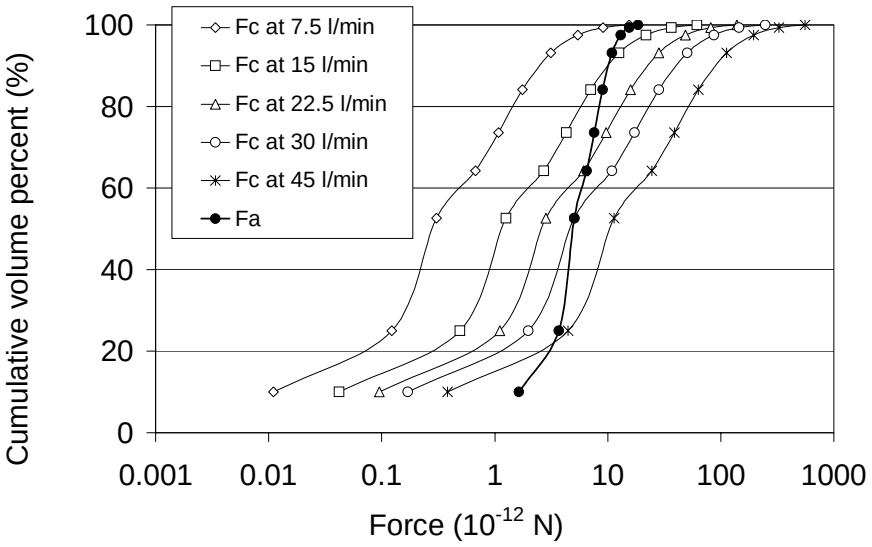

Figure 4.2. Presentation of the Force Distribution Concept (FDC): comparison of the size distributions of centrifugal separation forces in the classifier at five different flow rates with adhesive forces in the mixture. See text.

Because of the great variety 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, neither of differences between the air and carrier particle velocities inside the classifier chamber (relevant to the calculation of F_C). However, absolute numerical values for the forces are not necessary. FDC has been developed to explain the changes in the force distribution curves relative to each other as the result of changing certain conditions during mixing and/or inhalation (preferably only one at the time), which results in widening (or narrowing) of the distribution curve(s) and/or a shift along the X-axis. These changes can be monitored with the carrier residue after inhalation. Carrier residue (CR) measurements (described in paragraph 2.2) are therefore part of FDC.

The carrier residue (CR) is a measure for the Y-coordinate of the intersection of both force distribution curves. If the separation forces are relatively low compared to the adhesive forces (as in Fig. 4.2 for F_C at 7.5 and 15 l/min), the Y-coordinate 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 the example in Fig.

4.2, the Y-coordinate at 45 l/min is only 22%. Consequently, CR at 45 l/min will also 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 (when the same drug sample is used), 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 however, e.g. by agglomeration of drug particles (increased drug particle inertia). Some practical applications of FDC will be discussed more in detail in this, and in next chapters.

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. 4.3. 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 (as in Fig. 4.1). One of the air channels also serves as powder channel.

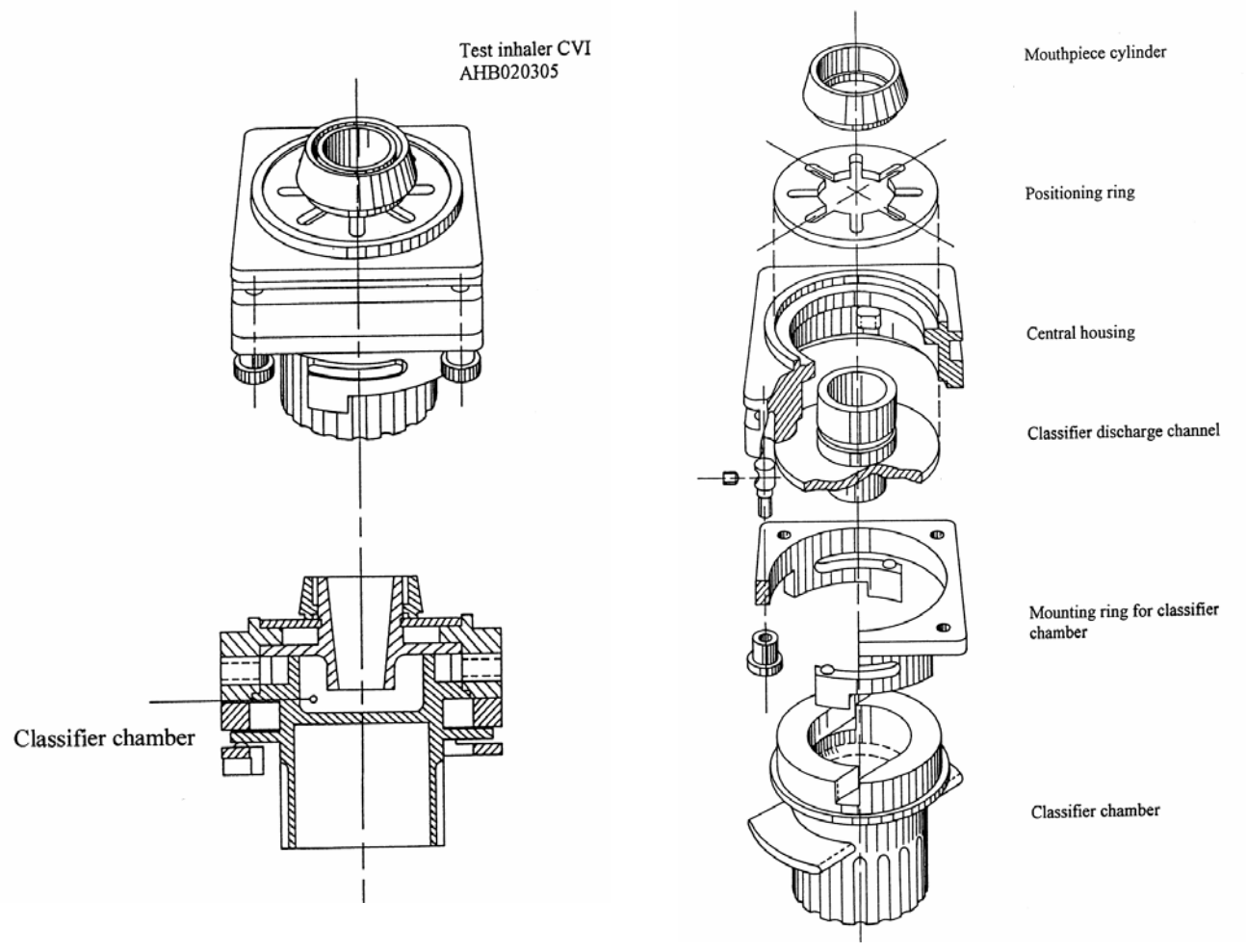

Figure 4.3. Presentation of a test inhaler with a basic air classifier concept.

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. The discharge channel with slightly increasing inner diameter towards its exit has 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. 4.3 has no integrated dose (measuring) system. Doses have to be inserted manually or be dispensed from a separate dose measuring principle that can be connected to the test inhaler. Retained carrier particles can be collected for analysis by disassembling the classifier chamber. Our air classifier technology already finds application in many different (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 results from these studies have been used. This has the consequence that some figures shown in this chapter (e.g. Figs. 4.5 and 4.6) represent many different formulations and size fractions of lactose. The experiments were selected such however, 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 sulfate (Duchefa Farma, The Netherlands). Double micronisation of the drug by jet milling (GfM, Germany), followed by 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 diameter of 2.14 μm (from laser diffraction characterisation). Budesonide for the carrier residue experiments was supplied as a free sample by Sofotec (Germany) in a size distribution with 10% < 0.54 μm and 100% < 4.60 μm (X_{50} = 1.04 μm), also measured with laser diffraction analysis (HELOS Compact KA with RODOS disperser, Sympatec, Germany). The budesonide was screened through a 90 micron sieve to break-up (or remove) hard agglomerates before making the adhesive mixtures. Carrier materials were Capsulac 60 (Meggle, Germany), Pharmatose in different grades (DMV International, The Netherlands) and special carrier size fractions (prepared from different Pharmatose types). All special 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 20 min vibratory sieving (Analysette 3, Fritsch, Germany), followed by 20 min air jet sieving (A200, Alpine, Germany). All fractions were characterised with laser diffraction technique (e.g. check upon the amount of adhering fines).

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 to 25 mg) per mixture. The samples were dissolved in 15 to 20 ml of 100% ethanol. The drug solutions were separated from the lactose crystals with a centrifuge (5 min at 3000 rpm; Rotana 3500, Hettich, Germany) and diluted (if necessary) before the drug concentrations were measured with a spectrophotometer at 242.8 nm (PU 8720 UV/VIS, Philips, The Netherlands).

3.4. Cut-off and retention efficiency experiments

For the carrier cut-off experiments, colistin sulfate was mixed with a small amount (16.7% by weight) of a special lactose size fraction (150-200 μm, derived from Pharmatose 100 M) which acts 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 the test inhaler was connected to a special inhaler adapter (INHALER 2000^{TM}, Sympatec, Germany) for laser diffraction analysis of the emitted particles (de Boer et al., 2002). The experimental cut-off diameters given equal the X_{100}-values of the emitted aerosols.

Carrier retention efficiency results at two different flow rates (Fig. 4.5A), have been derived from different studies (for reasons explained in Paragraph 3.1). Different size fractions of Pharmatose (as carrier) were used and budesonide concentrations varied between 0.4 and 1%.

For the percent carrier passage (equals 100 minus percent retention) as function of inhalation time (Fig. 4.5B), 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. 4.5C (the effect of dose weight on percent carrier passage), different amounts of Pharmatose 325 M (without drug) were added to the classifier chamber. Each data point in Figs. 4.5A and B (from cascade impactor experiments) is the mean of 2 series of ten inhalations each; in Fig. 4.5C, each data point represents a single inhalation experiment.

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

A glass constructed four stage cascade impactor (MSLI of the type described by Hallworth and Andrews, 1976) was used to measure the fine particle fraction (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 second impactor stage has theoretical cut-off diameter values for unit density spheres of 15.15 and 10.71 μm at 30 and 60 l/min respectively. The impactor was operated in combination with a dry bent inlet tube with large radius (to avoid de-agglomeration of powder within this induction 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. 4.6) is the mean of two series of ten inhalations. For the carrier residue measurements, of which the results are presented in the Figs. 4.7 and 4.8, the test inhaler was connected to a small wash bottle (single shot impinger) to reduce the volume (which influences the flow increase rate through the inhaler) between the test inhaler and the solenoid valve. After each inhalation, the retained carrier particles were 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 experiments, CR is expressed as percent of the original carrier payload and corrected for a minor carrier discharge from the classifier during inhalation (by linear extrapolation to 100% retention). The CR values presented in Fig. 4.7 are the mean of 3 inhalations; the results in Fig. 4.8 have been averaged for two series of five inhalations each.

3.6. Laser diffraction experiments

For determination of the classifier cut-off diameters, a prototype inhaler adapter (University of Groningen) was applied. Size distributions of the drugs and carrier materials were measured with a COMPACT/KA laser diffraction apparatus (Sympatec Germany). Lenses of 100 or 200 mm lens were selected (depending on the size distribution to be

measured) and calculations were made with the Fraunhofer theory. Drugs and carrier materials were dispersed with a RODOS dry powder disperser at 3 or 5 bar.

For laser diffraction analysis (lda) of the aerosol cloud from the test inhalers (Figs. 4.9 and 4.10), an INHALER 2000^{TM}-adapter was used in combination with a HELOS/BF-MAGIC laser diffraction apparatus (Sympatec, Germany). 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 with opening of the solenoid valve; measurements were stopped after 3 s of inhalation. Because of an increasing window pollution with increasing inhalation time, only the data from the first 2 s have been used.

4. Results and discussion

The airflow resistance of the basic classifier is 0.051 kPa$^{0.5}$.min.l^{-1}. This high resistance confines the maximal flow rate (that can be achieved by a patient) through this inhaler to a value of approximately 60-75 l/min (corresponding with 10 and 15 kPa respectively). Testing at higher flow rates is not necessary. Fig. 4.4 shows that the theoretical cut-off diameter of this concept 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 the drug particles (in the size range that is relevant to lung deposition), and low enough to expect effective retention of carrier particles of 30 μm or larger.

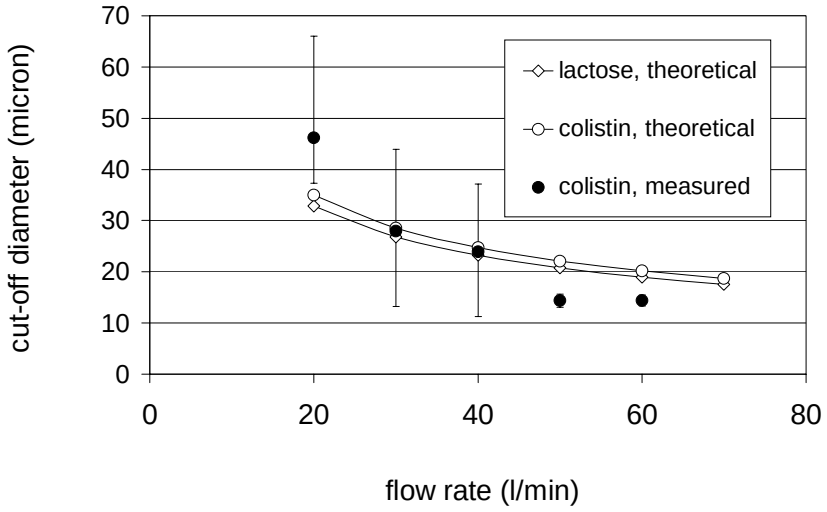

Figure 4.4. Theoretical and experimental cut-off diameters of the basic air classifier as function of the inspiratory flow rate for colistin sulfate. The bars, in connection with the measured values, indicate the maximum and minimum values obtained.

The experimental cut-off diameters in this figure correspond fairly well with the theoretical values for colistin sulfate, although a certain discrepancy may be expected for a number of reasons. Most of all, the order of magnitude of various side effects can not 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 re-bounced 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 is 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.

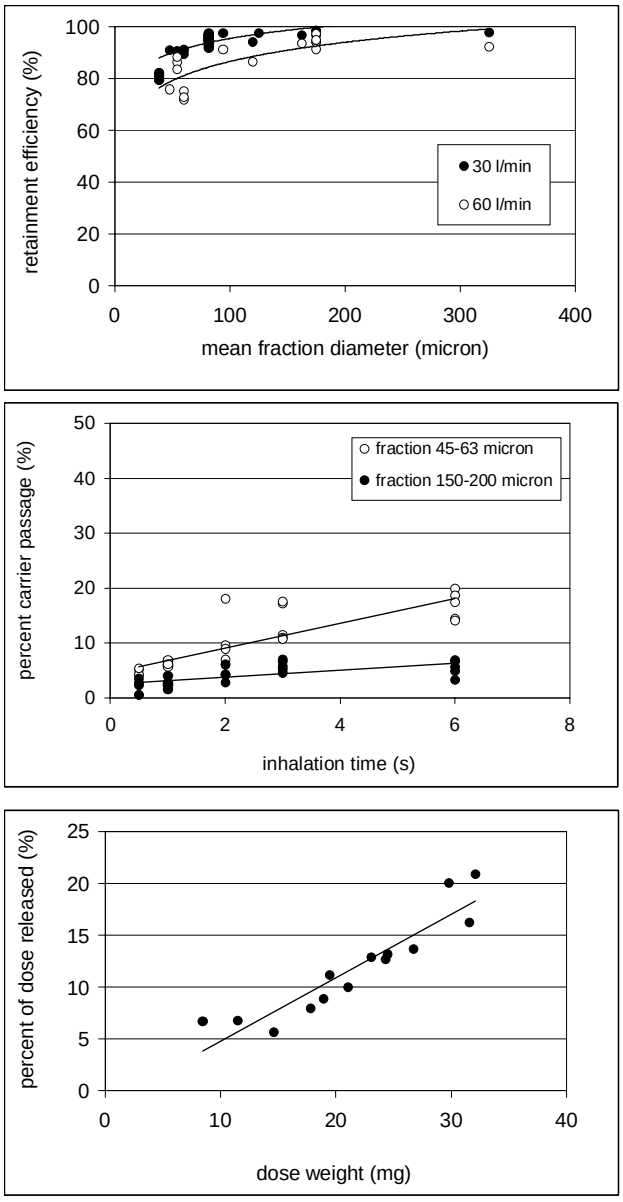

Figure 4.5A. Carrier retention (withdrawal) efficiency (as percent of dose) as function of mean fraction diameter for size fractions from different types of Pharmatose at two different flow rates. Dose is 25 mg; inhalation time is 3 s. B. Carrier passage (as percent of dose) from the test inhaler as function of the inhalation time for two different size fractions derived from Pharmatose 150 M (45-63 μm) and Capsulac 60 (150-200 μm) respectively at 60 l/min. Dose is 25 mg. C. Carrier release from the classifier (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.

The carrier retention efficiency is presented in the Figs. 4.5A-C. Fig. 4.5A 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 micron at 60 l/min, respectively > 150 μm at 30 l/min. The percent of retained carrier particles also depends on the inhalation time (Fig. 4.5B). Passage of particles larger than the theoretical cut-off diameter is a random occurrence, as has been explained in the discussion of Fig. 4.4. 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. 4.5A: the percent of carrier passage at the same flow rate and inhalation time increases with decreasing mean carrier particle diameter. The number of particle-particle collisions per unit time also increases with increasing carrier payload. Therefore, acceptable retention values for the classifier in the presented test inhaler (> 90%) require that the dose weight is below 20 mg (Fig. 4.5C).

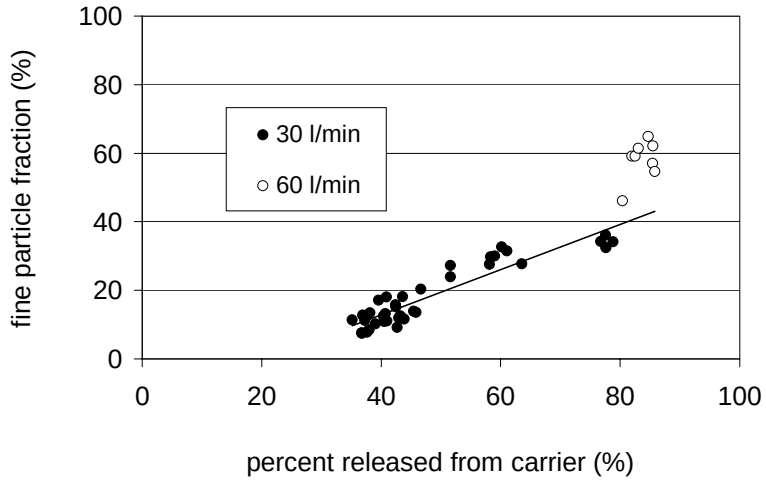

Figure 4.6. Fine particle fraction (fpf) versus percent drug released from carrier (100-CR), both as percent of real dose, for different formulations (carrier size fractions) with 0.4 to 1% of budesonide at two different flow rates. Test inhaler: Fig. 3.5; inhalation time is 3 s.

Fig. 4.6 shows that fine particle fraction (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 to 1% budesonide and different carrier size fractions. For all mixtures, fpf is substantially lower than the corresponding percent of drug released from carrier, in spite of the fact that practically all detached particles are within the fpf as defined (having a high upper class limit of 10.7 μm at 30 l/min for the cascade impactor used). Also 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 (when this is a liquid impinger). Some of these losses are the result of electrostatic effects which vary with circumstances (e.g. relative humidity of the air, the number of preceding inhalations, cleaning procedures). They can only partly be controlled. Such losses contribute to a 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 fine particle fraction is different for 30 and 60 l/min, as shown in Fig. 4.6. These losses are one of the reasons why we prefer to rely on percent carrier residue values for formulation studies, rather than on fine particle fractions. There are two other reasons for this preference. Firstly, carrier residue measurements are much less laborious and time consuming than cascade impactor experiments and they yield reliable information based on single inhalations. Secondly, carrier particles discharged from a dry powder inhaler (dpi) collide with the inner wall of the induction port where they enter the sharp 90 degrees 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 and extent of the contribution is 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 fine particle fraction. This can be observed with laser diffraction analysis of the aerosol cloud (de Boer et al., 2001). The effect occurs particularly at lower flow rates (< 30 l/min), when inertial separation forces are sufficiently high to detach such agglomerates (with much higher inertia than single particles) from the carrier crystals, but dispersion 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 chapters 6 and 7.

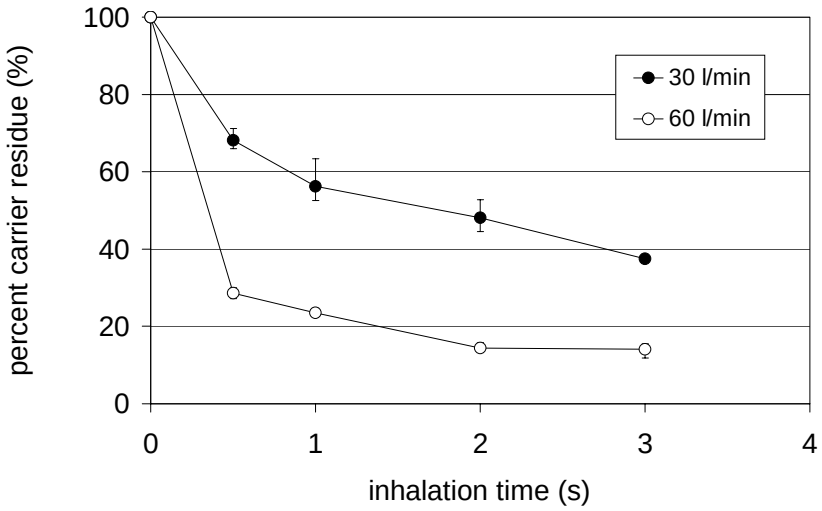

Figure 4.7. Percent carrier residue (CR), extrapolated to 100% retention, obtained with the test inhaler (Fig. 3.5) as function of flow rate (30 and 60 l/min) and circulation time for an adhesive mixture with 2% budesonide and Capsulac 60 as carrier. Dose is 10 mg (n=3). The spread bars indicate the maximum and minimum values obtained.

Fig. 4.7 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 carrier residue 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 in a classifier by increasing the inhalation time from 0.5 to 3 s. The spread bars 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 halve second, which results in a release of 51% of the 'end value' (after 3 s) at 30 l/min versus 83% at 60 l/min. Meaning 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. 4.7 are important for classifier design and optimisation of the inhaler system (which includes the adhesive mixtures to be used in this inhaler) regarding the desired carrier residence time (within the classifier). This aspect will be discussed more in detail in the next chapters of this thesis.

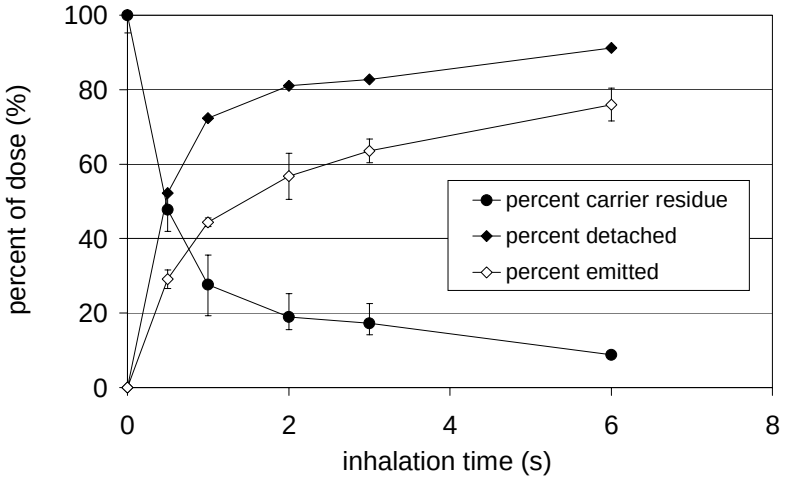

Figure 4.8. Percent carrier residue (CR), percent drug detached (100 - CR) and percent emitted (100 - CR - IA) as function of inhalation time for a mixture with 4% budesonide and carrier size fraction 150-200 μm (from Pharmatose 150 M) obtained with the test inhaler (Fig. 3.5) at 60 l/min. IA is the percent of dose accumulated in the inhaler. The spread bars indicate the maximum and minimum values obtained.

Fig. 4.8 compares the percent carrier residue, 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 (Fig. 3.5), as this device was designed primarily for carrier residue measurements. Good knowledge of the detachment and dose emission rates (first derivatives of the curves in Fig. 4.8) are relevant to the design of classifiers, as well as to understand the underlying mechanisms for particle-to-particle interactions.

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. 4.9 shows the optical concentration of the aerosol cloud from the test inhaler (Fig. 3.5) as function of the inhalation time for the same formulation as presented in Fig. 4.8. The areas under the curve (AUC) have been calculated for each time interval (0.02 s) and processed into a cumulative AUC-curve as function of the inhalation time. The sum of all AUC-values (up to and

including 2 s) has been equated with the percent of dose emitted from the test inhaler (56.77% after 2 s in Fig. 4.8). Next, the cumulative AUC-curve for the optical concentration has been recalculated into a curve presenting the cumulative 'percent of drug detached from carrier' as function of the inhalation time.

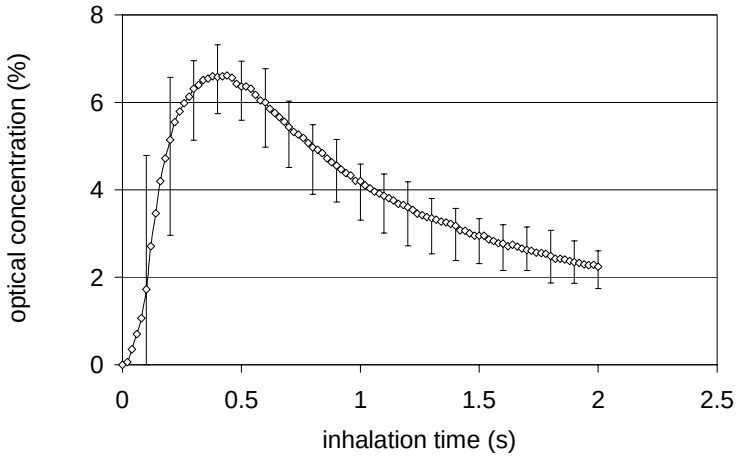

Figure 4.9. Optical concentration of the aerosol cloud from the test inhaler (Fig. 3.5) as function of the inhalation time for the same mixture and the same inhalation conditions as presented in Fig. 4.8. The spread bars indicate the maximum and minimum values obtained.

This curve is shown in Fig. 4.10, in comparison with the emission rate curve from carrier residue measurement. To check whether there really exists a proportional correlation between the particle concentration in the aerosol and the measured optical concentration, different suspensions with increasing concentration of the same particle size fraction in saturated liquids were made. Confinement of the emission time to two seconds has been for practical reasons; at longer times, necessary corrections for window pollution appeared to be too extreme.

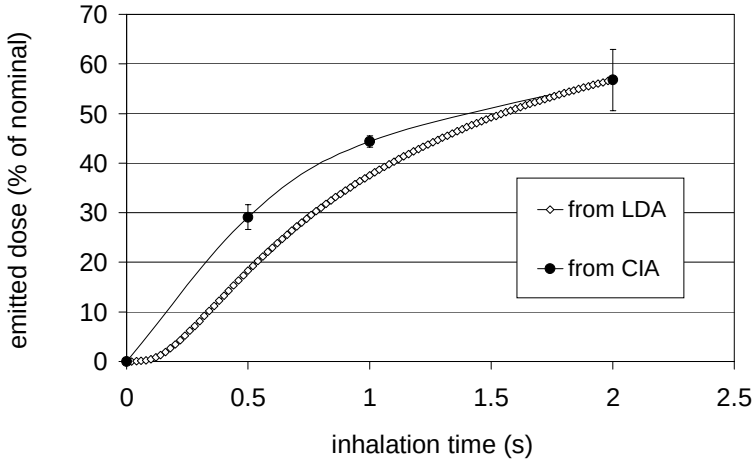

Figure 4.10. Comparison of detachment rate obtained from two different techniques (lda and carrier residue measurement); data derived from the Figs. 4.8 and 4.9. The spread bars indicate the maximum and minimum values obtained.

Although both curves obtained from lda and carrier residue 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. 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 the distance between the classifier and the laser beam before they are measured. It may not be surprising the 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) force distribution concept (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 halve second of inhalation is obtained from optical concentration measurement of the aerosol cloud with laser diffraction technique.

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