The Mode of Drug Particle Detachment from Carrier Crystals in an Air Classifier–Based Inhaler

Anne H. de Boer,[1,4] Paul Hagedoorn,[1] Doetie Gjaltema,[1] Dorette Lambregts,[2] Meike Irngartinger,[3] and Henderik W. Frijlink[1]

Purpose. To investigate the mode of drug particle detachment from carrier crystals in an air classifier as a function of the carrier size fraction, payload, and the circulation time in the classifier.

Methods. Laser diffraction analysis of the aerosol cloud from the classifier has been performed at 10, 20, 30, and 60 l/min, using a special adapter, for different adhesive mixture compositions.

Results. A significant part of the drug particles is detached from carrier crystals during inhalation as small agglomerates. Such agglomerates originate from the starting material or are newly formed on the carrier surface during mixing. The degree of agglomeration during mixing depends on the carrier size, payload, and surface rugosity. The size of the agglomerates that are formed during mixing, increases with the size of the carrier particles. Predominantly the largest drug particles and agglomerates are detached within the first 0.5 s of inhalation. After 0.5 s, smaller primary particles are dislodged.

Conclusions. A high ratio of removal forces to adhesive forces causes a high drug detachment rate from carrier crystals in a classifier within the first 0.5 s of inhalation. The high ratio can be explained by dislodgment of agglomerates and the largest primary particles in the early phases of inhalation. At higher flow rates, detached agglomerates may be further disintegrated into primary particles before they are discharged from the classifier. Agglomeration of drug particles on the carrier surface is the result of the same forces that are responsible for pressing these particles firmly to the carrier crystals during mixing.

KEY WORDS: adhesive mixtures; air classifier; dry powder inhalers; laser diffraction analysis; mode of detachment.

INTRODUCTION

In a previous study, the rate of drug particle detachment from carrier crystals during inhalation with a basic air classifier has been presented (1). It was discussed that the rate may depend on how drug particles are dislodged: as primary particles or as small agglomerates. Therefore, it was concluded that studying the mode of detachment as function of the inhalation time is necessary. This includes investigation of the manner in which drug particles are attached to the carrier surface during mixing. Very little has been reported in this respect. It has been described that drug particles tend to form particle agglomerates (layers) on the carrier crystals at concentrations well below that for a monolayer on the carrier surface (2). Strong clusters are formed that can be dislodged from the carrier as a whole. In the same study, it was also described that the fine particles are likely to fill up carrier surface irregularrities rather than to cover the surface. This idea was confirmed quite recently (1,3). In a study on ternary mixtures with micronized drug and lactose (4), it was proposed that multilayer associations of fines increase the drug detachment from the carrier surface due to an increased mass of detached agglomerates. The latter is in agreement with theoretical expectations for de-agglomeration principles using inertial removal forces (5). This proposal also finds support from the investigation of the mode of drug detachment from surfaces following deposition from aerosol streams (6). It was observed that drugs that accumulate as aggregates on model surfaces detach under the application of a centrifugal force either as one large aggregated mass or as smaller agglomerates, depending on the primary drug particle size.

Increasing the diameter of an adhering particle (d) increases the ratio of an inertial removal force ($F_R \propto d^3$) to the adhesive force ($F_A \propto d^1$) acting on this particle and, thereby, the chance of being dislodged (1,5). Proof for this has been given for single drug particles using budesonide samples with different size distributions (7). But it has never actually been shown that size enlargment of the drug by agglomeration on the carrier surface increases the degree or rate of detachment. Nor has it been investigated what are the consequences of drug agglomeration for the size distribution in the aerosol from the inhaler. The aim of this study is to investigate the mode of detachment for drug particles from carrier crystals in an air classifier based inhaler as function of the carrier size fraction and carrier payload. Time-sliced measurements have been performed to relate this mode of detachment to the previously presented rate of detachment (1). The degree of agglomeration has been related to the size and effectivity of press-on forces acting during the mixing process. Good knowledge of the degree of agglomeration on the carrier surface during mixing, as well as of the strength of these agglomerates, is necessary to optimize formulations and production processes and to develop further air classifiers as de-agglomeration principle for dry powder inhalers (5).

MATERIALS AND METHODS

Materials

Alpha lactose monohydrate carrier fractions were obtained by subsequently 20 min vibratory sieving (Analysette 3, Fritsch, Idar-Oberstein, Germany) and 20 min air jet sieving (A200, Alpine, Augsburg, Germany), using Pharmatose 80M (fraction 250–355 μm) and 150M (fractions 45–63 and 150–200 μm) as starting materials (DMV International, Veghel, The Netherlands). Micronized budesonide was supplied by Sofotec (Frankfurt, Germany).

Adhesive Mixture Preparation and Characterization

Adhesive mixtures with different budesonide concentrations (% w/w) and different carrier fractions were prepared in

[1] Department of Pharmaceutical Technology and Biopharmacy, Groningen University Institute for Drug Exploration (GUIDE), 9713 AV Groningen, The Netherlands.
[2] DMV-International, Veghel, The Netherlands.
[3] Sofotec GmbH, Frankfurt, Germany.
[4] To whom correspondence should be addressed. (e-mail: A.H.de. Boer@farm.rug.nl)

ABBREVIATIONS: CC, carrier coverage, coverage of the carrier surface as percent of a monolayer of drug particles; CR, carrier residue, residual drug still attached to carrier after inhalation as percent of the initial payload; k, detachment rate constant; $k_{0.5}$, detachment rate constant in the first 0.5 s of inhalation.

a stainless steel mixing container of 160×10^{-4} m^3 using a tumbling mixer (Turbula T2C, WA Bachofen, Basel, Switzerland) at 90 rpm. The mixing time was 10 min and the batch size 25 g. The budesonide was screened through a 90-μm sieve prior to mixing in order to break up large agglomerates in the powder. Mixture homogeneity was determined on 20 samples of 25 mg each. The samples were dissolved in 20 ml of ethanol analytical grade. The solutions were cleared from nondissolved lactose carrier particles in a centrifuge (Rotana 3500, Hettich, Tuttlingen, Germany) during 5 min at 3000 rpm, and drug concentrations were measured with a spectrophotometer (PU 8720 UV-VIS, Philips, Eindhoven, The Netherlands) at a wavelength of 242.8 nm.

Carrier Residue Measurements

Carrier residue experiments were performed with an air classifier–based test inhaler of which the working principle and the procedures for use have been described previously (5). The test inhaler consists of a powder de-agglomeration principle only and has no dose (measuring) mechanism. For the carrier residue (CR) experiments, the test inhaler was connected to an impactor of the Fisons type of which the third (instead of the fourth) stage was in connection with the vacuum system. This, to reduce the air flow resistance and volume of the test arrangement, so as to reduce the time within which the desired stationary flow rate through the inhaler is established. The flow maneuver through the inhaler was controlled with a previously adjusted flow controller and a solenoid valve connected to a timer. For each investigated condition, five doses of 25 mg were inhaled. After each experiment, retained carrier particles were removed from the classifier and analyzed upon residual drug, using the same procedures as described for homogeneity testing of the mixtures.

Laser Diffraction Experiments

For the laser diffraction experiments, a HELOS BF-MAGIC with standard Windox software (Fraunhofer calculation in the LD mode) was used (Sympatec, Clausthal-Zellerfeld, Germany). All measurements were performed with a 100-mm lens. The size distribution of the budesonide was obtained from RODOS dispersion at 5 bar (n = 2). For the experiments (dose is 25 mg; n = 5), the same test inhaler was used as for the carrier residue measurements. The inhaler was connected to a previously described inhaler adapter (8) through which a minor counter flow was applied. Because the test inhaler has nearly complete carrier retention, the use of a pre-separator was not necessary. Different circumstances during the laser diffraction experiments required different procedures and adjustments.

For the Figs. 2 to 4 and 6, flow adjustment and reference measurements were conducted with the same amount (25 mg) of carrier fraction (no drug) inside the classifier to correct for released lactose fines.

For Fig. 6 (time-sliced measurements), start of the laser diffraction measurement was synchronized with opening of the valve, starting the flow rate through the inhaler. Total measuring time was 1 s, and each measurement was split into steps of 50 ms. Each data point is the mean of 5 doses.

Calculations

For calculation of the percent carrier coverage with budesonide particles, it was assumed that all drug particles are spherical and monodisperse (particle diameter equals the median diameter from laser diffraction analysis). A real density of 1240 kg/m^3 for budesonide was used. It was also assumed that the projection area of a single particle is that of a square with the same side as the diameter of the sphere and that there is no space between the squares. Total surface area of the carrier particles was derived from the lactose density (1540 kg/m^2) and the arithmetic mean of the sieve fraction, assuming also that these particles are spherical. There is an inaccuracy in these calculations from the shape factors of particularly the carrier particles, but because these factors are more or less the same for all fractions used (as checked with scanning electron microscopy) the inaccuracy does not lead to incorrect interpretations for comparative experiments.

For calculation of the X_{50}-value in the aerosol from the classifier (at 60 l/min) after exclusively the largest primary drug particles have been detached during the early phase of inhalation (first 0.5 s) from a mixture with carrier size fraction 45-63 μm and 4% budesonide (Fig. 7), previously presented detachment rates have been used (1). The cumulative fractions detached within 0.1 s and 0.2 s of inhalation (7.99% and 27.69% respectively), were subtracted from the top of the cumulative size distribution curve obtained from RODOS dispersion at 5 bar, ranging from < 0.9 to 10.5 μm. This yielded remaining fractions of 92.01% (for the size range < 0.9 to 3.25 μm) and 72.31% (for the size range < 0.9 to 2.12 μm) respectively. Next, new cumulative size distribution curves were calculated for the separated (subtracted and remaining) fractions, yielding X_{50}-values by intrapolation. Such calculations are only possible when sufficient size classes in the subsequently subtracted fractions are available. This is not the case for fractions derived from the steepest part of the size distribution curve (particles < 2.12 μm). Therefore, it was assumed that the phase during which specifically the largest particles are dislodged lasts only 0.2 s, and that particles of remaining sizes are detached randomly, yielding a constant size distribution in the aerosol for t > 0.2 s. Obviously, this is a simplification of reality but it provides a good starting point for comparison with experimentally obtained data.

RESULTS AND DISCUSSION

The Rate of Drug Particle Detachment

To study the rate of drug particle detachment from carrier crystals in an air classifier, a budesonide sample with a volume median diameter of 1.04 μm was used (1). It could be shown that the detachment rate approaches fairly well first order kinetics for the first half second of inhalation. The rate constant decreased strongly with increasing carrier diameter however, and even more strongly with the fraction of drug already dislodged. This indicated that the rate is not solely determined by the drug concentration on the carrier surface (as expected for a first order detachment). It was concluded that the rate constant k is a function of the ratio of removal forces (F_R) to adhesive forces (F_A) at any moment during inhalation. Therefore, the fact that the constant decreases with the inhalation time, and with the carrier diameter as well,

is either a result of a decreasing F_R, or an increasing F_A, or both.

The budesonide in this new study has a volume median diameter (X_{50} from laser diffraction analysis) of 1.45 μm (X_{10} = 0.65 μm; X_{90} = 2.97 μm). To make a fair comparison between both studies, some release rate experiments have been duplicated with this new drug sample. The results are shown in Fig. 1. In this figure, the rate constant is presented as function of the mean carrier diameter. The results (trends) are in good agreement with those reported previously (1) in spite of the small difference in size distribution for the drug. The rate constant within the first half second of inhalation ($k_{0.5}$) decreases almost linearly with the mean carrier diameter (for both levels of carrier coverage). As before, a strong reduction in k after the first half-second of inhalation is obtained. The results confirm the data of Dickhoff *et al.* (9) who found an increasing amount of residual drug on carrier after inhalation (CR: carrier residue) with increasing carrier payload for coarse carrier fractions. They also obtained a decreasing CR for fine carrier fractions after 3 s inhalation at 30 l/min. Considering the finding that a major fraction of drug is detached in the first 0.5 s of inhalation (1), it may be expected that a higher $k_{0.5}$ leads to a lower CR after 3 s inhalation and *vice versa*. This difference in behavior between different carrier fractions was attributed to a higher excess of drug particles relative to the active (carrier) sites when the carrier payload is increased for fine carrier particles. There is also a higher effectivity of inertial and frictional press-on forces during the mixing process for coarse carriers. After saturation of the active sites, the mean adhesive force becomes less for mixtures with fine carrier particles. Such active sites are frequently carrier surface irregularities inside which drug particles can find shelter from the press-on forces (9). Therefore, saturation of these irregularities results in a higher effectivity of the press-on forces, which has the effect of a higher mean adhesive force with increasing carrier payload for mixtures with coarse carrier particles. As already discussed in the introduction a high carrier payload could also promote drug
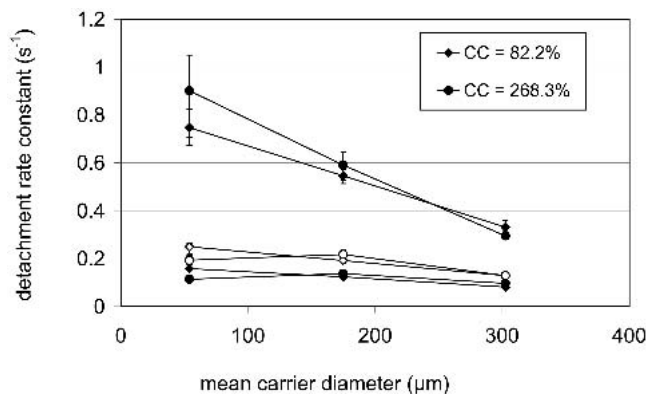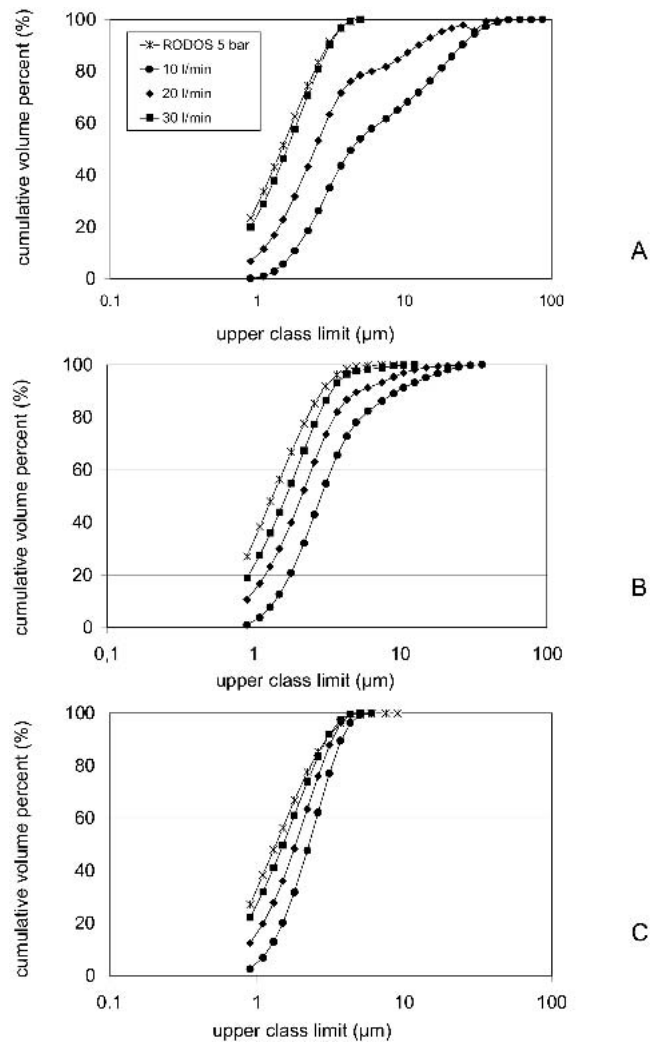

Fig. 2. Cumulative volume distribution curves as function of particle diameter (from laser diffraction analysis) for aerosols from an air classifier–based inhaler for mixtures with 4% budesonide and different carrier size fractions 250–355 μm (A); 150–200 μm (B), and 45–63 μm (C), respectively. Flow rates: 10, 20, and 30 l/min. For comparison, the size distribution of the drug obtained with RODOS dispersion (5 bar) is given, too. Symbols (explained in Fig. 2A) are the same for all figures. All curves are the mean of five doses of 25 mg. The maximal and minimal values obtained for the X_{50}-values are given in Table I.

particle agglomeration on the carrier surface (1,2,4). This increases the mass of the particles to be detached and by that the removal force (F_R). All these variables affect the release rate constant k ($\propto F_R/F_A$), but it cannot be concluded whether a change in k is the result of a change in either force (F_R or F_A) alone or of both forces to different extents. This information may be obtained from studying the mode of drug particle detachment during inhalation.

The Mode of Drug Particle Detachment

Figures 2A–2C show the cumulative size distribution of the aerosol from the classifier based inhaler at 10, 20, and 30 l/min, in comparison with that of the budesonide obtained from RODOS dispersion at 5 bar. The size distribution curves obtained for different carrier size fractions differ most at the

Fig. 1. Detachment rate constant (k) as function of mean carrier diameter for mixtures with carrier fractions 45–63; 150–200, and 250–355 μm inhaled from a classifier-based test inhaler at 30 l/min. Each fraction was prepared with two different carrier payloads, yielding the same percentages of carrier coverage (CC) of 82.2% and 268.3%, respectively. The two upper lines are for the constants within the first half second of inhalation ($k_{0.5}$); the two middle lines (open symbols) are for 3 s (k_3); and the two lower lines for 6 s circulation (k_6). The spread bars indicate the highest and lowest value obtained (n = 5).

lowest flow rate of 10 l/min. At this low flow rate, the ratio of average removal force to average adhesive force is quite low (5). Only the particles with the highest removal forces can be dislodged, which most likely are the particles with the highest mass. For the finest carrier fraction (Fig. 2C), this must predominantly be the largest primary drug particles, as the X_{90}-value of the aerosol at this flow rate (3.75 μm) equals 97.5% of the cumulative volume curve from RODOS dispersion, which yields the primary particle size distribution. This indicates that hardly any agglomerates have been formed during mixing. On the other hand, the X_{90}-value for the coarsest fraction is 24.68 μm. This is considerably higher than even the X_{100}-value of the primary drug particles from RODOS dispersion at 5 bar (9 μm). This confirms that drug particle agglomeration has occurred on the carrier surface (2). The results also show that the degree of agglomeration depends on the carrier particle mass. The mixture with carrier fraction 150–200 μm has an intermediate X_{90}-value of 9.76 μm at 10 l/min. At higher flow rates, the size distribution in the aerosol from the classifier shifts toward that of the primary drug particles. The reasons for this shift are a further breakup of the detached agglomerates (mainly for the coarse carrier fractions) and an increased dislodgement of smaller primary drug particles (for all carrier fractions). The breakup of detached agglomerates is the second step of a two-step de-agglomeration process in a classifier.

Drug Particle Agglomeration on the Carrier Surface During Mixing

Drug particle agglomeration on the carrier surface is promoted by inertial and frictional forces. These forces result from carrier particle collisions and relative displacements during the mixing process. Figure 3 compares the frequency distributions of particle diameters in the aerosol cloud at 10 l/min for the mixtures of Figs. 2A–2B in comparison with that from RODOS dispersion at 5 bar. The aerosol cloud from the mixture with carrier fraction 250–355 μm has clearly a bimodal distribution, and the peak of the agglomerates is around 21 μm. The curve for the mixture with fine carrier (45–63 μm) does not show a second peak for agglomerates and approaches that of the distribution curve obtained from
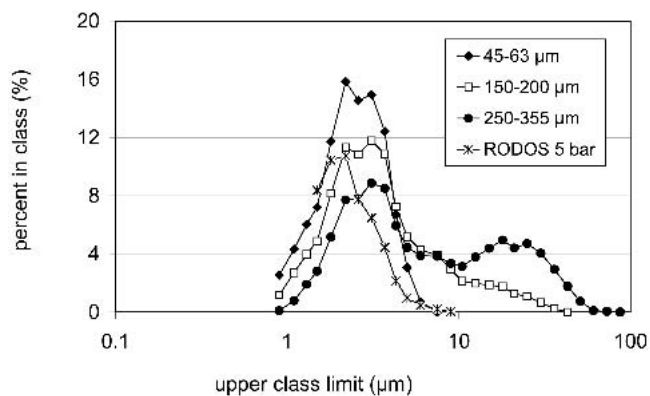

Fig. 3. Comparison of the volume frequency distribution curves at 10 l/min, derived from Figs. 2A–2C, showing the size distributions of dislodged agglomerates from different carrier size fractions (4% payload) in comparison with that of the primary drug particles from RODOS dispersion.

RODOS dispersion. Estimating that the porosity of a dislodged agglomerate is 48% (cubic ordering of the primary particles within the agglomerate), a cluster of 21 μm could contain more than 1500 primary drug particles with a median diameter of 1.45 μm. Meaning that the mass of such an agglomerate is nearly 1500 times the mass of a median-sized primary drug particle. As explained before, drug particle agglomeration increases the removal forces acting on such agglomerates during inhalation. For the coarse carrier fraction (250–355 μm) with 4% drug, detached agglomerates at 10 l/min in the size class > 10 μm comprise 35% of total powder volume in the aerosol (Fig. 2A), whereas almost 50% of the particles is larger than 5 μm (Table I). For the fine carrier fraction (45–63 μm) with the same payload, the median diameter of detached particles is only 2.26 μm (Table I). Meaning that the average inertial removal force ($F_R \propto d^3$) for the particles detached from the coarse carrier is more than 10 times higher than F_R for particles dislodged from the fine carrier. Yet, the coarse carrier fraction with the highest degree of agglomeration, has the lowest initial release rate constant (Fig. 1) and the highest carrier residue (9). The detached fraction during inhalation from carrier fraction 250–355 μm at 4% payload (30 l/min) is less than 25%, whereas that from carrier fraction 45–63 μm at the same flow rate is nearly 55%. This can only be explained with an even greater increase in the average adhesive force (F_A) for the coarse carrier, which increase is the result of the same (press-on) forces during the mixing process that also promote drug particle agglomeration.

Breakup of Dislodged Agglomerates in the Classifier

Table I summarizes the X_{50}-values of the aerosol clouds for the mixtures in Figs. 2 and 3 (with 4% budesonide). At 30 l/min, the size distribution in the aerosol already approaches that of the primary drug particles (1.45 μm) for all carrier fractions. Without the secondary breakup of detached agglomerates in the classifier at higher flow rates, the particle size in the aerosol would be unfavourable for inhalation. Also, mixtures with 0.4% budesonide have been investigated at three different flow rates of 10, 20, and 30 l/min (Table II). Basically, the changes in the size distribution of the aerosol are the same as found for the 4% mixtures. At 10 l/min, the largest agglomerates are dislodged from the mixtures with the coarsest carrier fraction. Increasing the flow rate results in further breakup of these agglomerates before they are discharged from the classifier. Yet, there is a fundamental difference, as shown in Fig. 4. In this figure the results obtained at 10 and 30 l/min are compared for the 0.4% and 4% mixtures for the carrier size fraction 250–355 μm. The degree of disintegration in the classifier at 30 l/min of detached agglomerates is clearly lower for the 0.4% mixture than for the 4% mixture. Similar results were obtained for the other carrier size fractions (150–200 and 45–63 μm) in this study.

Natural Drug Agglomerates from the Starting Material

There may be a good explanation for the difference in breakup of dislodged agglomerates between both types of mixtures. At a low percent of carrier coverage, most drug particles are assembled in carrier surface irregularities where they are beyond reach of the frictional and inertial (press-on) forces which break them up during the mixing process

Table I. Volume Median Diameter (X_{50} from Laser Diffraction Analysis) of Particles in the Aerosol Cloud from the Test Inhaler at 10, 20, and 30 l/min for Mixtures with Different Carrier Size Fractions and 4% Budesonide[a]

	10 l/min	20 l/min	30 l/min
Fraction 45–63 μm	2.26 (2.18–2.35)	1.84 (1.78–1.94)	1.51 (1.39–1.63)
Fraction 150–200 μm	2.90 (2.84–2.99)	2.13 (2.05–2.33)	1.67 (1.56–1.74)
Fraction 250–355 μm	4.75 (3.75–6.25)	2.54 (2.13–3.05)	1.62 (1.60–1.66)

[a] Values between brackets indicate the maximal and minimal values obtained (n = 5).

(1,9,10). Such drug clusters include small agglomerates that are already present in the starting material, in spite of screening the drug through a 90-μm screen before mixture preparation. Unless these "natural" agglomerates are dislodged during the mixing process and repositioned on the carrier surface where they become in reach of breakup forces, they remain in an aggregated state. Their strength could be greater than that of newly prepared agglomerates on the carrier surface during mixing and, therefore, breakup after dislodgement in a classifier at 30 l/min could be less complete than that of the newly formed associations. This increases the X_{50}-value in the aerosol cloud (at 30 l/min), as shown in Table II and in Fig. 4. Proof for the existence of strong "natural" drug agglomerates in the starting material is given in Figs. 5. Figure 5A compares the cumulative volume distribution curves of pure drug obtained from RODOS dispersion (at 0.5 and 5 bar) with that from the classifier at different flow rates. Only at 5 bar (RODOS) are most of the "natural" agglomerates broken into primary particles. At this pressure, less than 1 volume percent of the drug comprises particles larger than 5 μm, whereas at 0.5 bar nearly 10% of the particles has a diameter of 5 μm or more. Inhalation of pure drug from the classifier at 60 l/min yields about the same size distribution as RODOS dispersion at 0.5 bar: slightly over 10% of the drug is larger than 5 μm. At 30 l/min from the classifier, this is nearly 13%. In the aerosol from the classifier (at 30 l/min) for mixtures with a coarse carrier fraction (250–355 μm) and 4% drug 100% is smaller than 5 μm. Also, from the mixture with carrier fraction 45–63 μm, only 2.5% is larger than 5 μm. So, in spite of extensive drug particle agglomeration on the carrier surface during mixing with coarse carrier particles (Fig. 3), particles in the aerosol produced at 30 l/min from such mixtures are finer than those obtained from pure drug at 60 l/min. This extends the relevance of the press-on forces to de-agglomeration of natural agglomerates during the mixing process. Figure 5B shows the sizes of released agglomerates (pure drug from the classsifier) at different flow rates.

Correlation Between the Mode and the Rate of Drug Particle Detachment

The action of the press-on forces during mixing (in terms of increasing the adhesive force) seems to provide a satisfactory explanation for the decreasing release rate constant with increasing carrier diameter (Fig. 1). But it cannot explain why the release rate falls so rapidly from the start of the inhalation for all carrier fractions. It was postulated (1) that this is the result of a strongly decreasing ratio of the removal force (F_R) to the adhesive force (F_A) for particles to be dislodged in subsequent order. Considering that the inertial removal force in a classifier is proportional to the third power of the particle diameter, whereas $F_A \propto d^1$, it could be that the largest particles (agglomerates) are detached first at a high rate, and that smaller particles for which the ratio of F_R to F_A is much smaller, probably even less than 1, follow next. According to this proposition, the mean particle size in the aerosol has to decrease with increasing inhalation time. Figure 6 obtained from time-sliced laser diffraction measurements shows that a decline for X_{50} and X_{90} with the inhalation time indeed exists for different carrier fractions (with 4% budesonide) during inhalation at 60 l/min. Initially (within the first 0.1 to 0.2 s of inhalation), the X_{50}- and X_{90}-values for the particles in the released aerosol are quite high compared to the corresponding values from RODOS dispersion at 5 bar (depicted as dotted lines). For the coarse carrier, detachment might be for agglomerates first and large primary particles next. The size of released agglomerates (particularly within the first 0.2 s of inhalation) is much smaller as shown in Fig. 3, which is the result of further disintegration of the agglomerates in the classifier at this high flow rate before they are discharged. For the fine carrier initial detachment could primarily be for the largest primary particles. As a result of the removal of specifically the largest particles first, the size distribution of the particles to be dislodged next is narrowed. Hence, X_{50} and X_{90} reach values below those obtained from RODOS dispersion at 5 bar.

To check whether this explanation in terms of sequential dislodgment it is plausible, the X_{50}-values for the particles in the aerosol from a mixture with carrier fraction 45–63 μm and 4% budesonide have also been computed. For the computations it has been assumed that particles detached within the first 0.1 and 0.2 s of inhalation are indeed exclusively the largest ones. Figure 7 shows these computed values as function of the inhalation time, in comparison with the experimentally found changes in X_{50} for the same mixture (copied

Table II. Volume Median Diameter (X_{50} from Laser Diffraction Analysis) of Particles in the Aerosol Cloud from the Test Inhaler at 10, 20, and 30 l/min for Mixtures with Different Carrier Size Fractions and 0.4% Budesonide[a]

	10 l/min	20 l/min	30 l/min
Fraction 150–200 μm	2.97 (2.68–3.12)	2.60 (2.48–2.79)	2.73 (2.70–2.78)
Fraction 250–355 μm	4.04 (3.31–4.69)	3.88 (3.79–4.04)	2.72 (2.65–2.76)

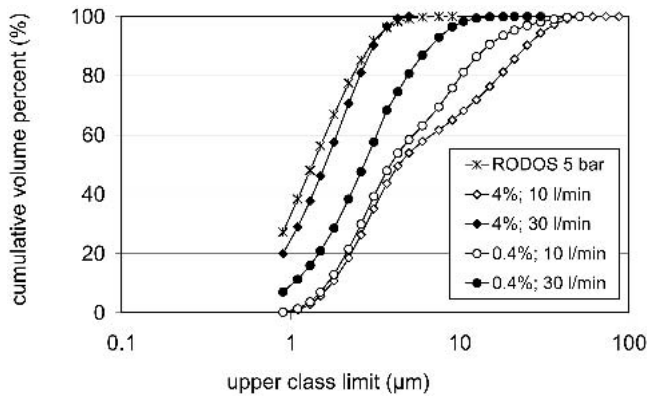[a] Values between brackets indicate the maximal and minimal values obtained (n = 5).

Fig. 4. Comparison of the cumulative volume percent curves as function of the particle diameter from laser diffraction analysis of aerosols from the classifier at two different flow rates (10 and 30 l/min) for mixtures with 0.4% and 4% budesonide, respectively, and carrier size fraction 250–355 μm (n = 3).

from Fig. 6). In spite of the simplifications and assumptions made for the calculations (see "Materials and Methods"), the computed curves in Fig. 7 indicate that the initial strong decrease in measured X_{50}-value can be explained with dislodgment of the largest particles only within the first 0.1 to 0.2 s. At longer times there is also a slight decline in the experimental X_{50}-value, showing that preferential dislodgment of the largest particles continues into the inhalation phase with
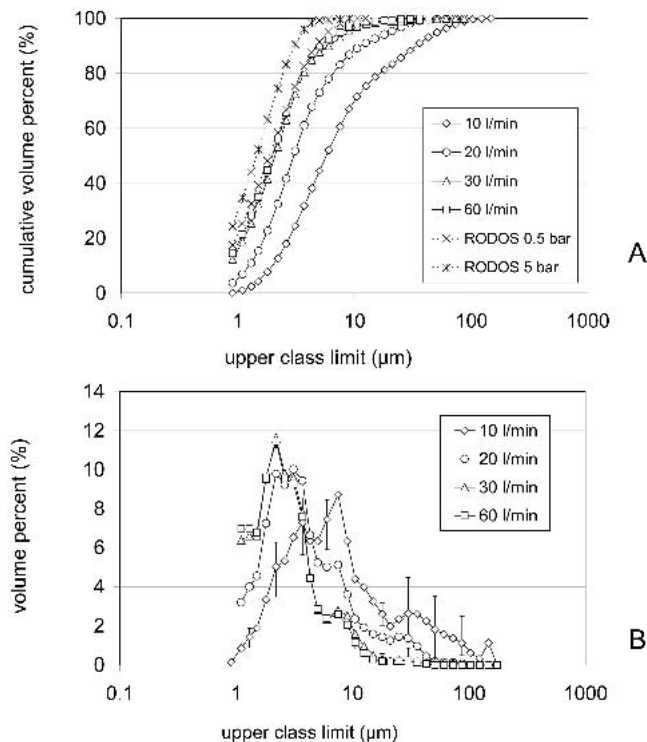

Fig. 5. Degree of breakup of natural drug agglomerates when pure drug (with sweeper crystals) is inhaled from the classifier-based inhaler at four different flow rates, respectively dispersed with a RODOS dry powder disperser at two different pressures. (A) The cumulative volume percent as function of the diameter. (B) The frequency distributions curves for the drug particle diameter in the aerosol from the classifier at different flow rates are compared to show the sizes of released agglomerates.
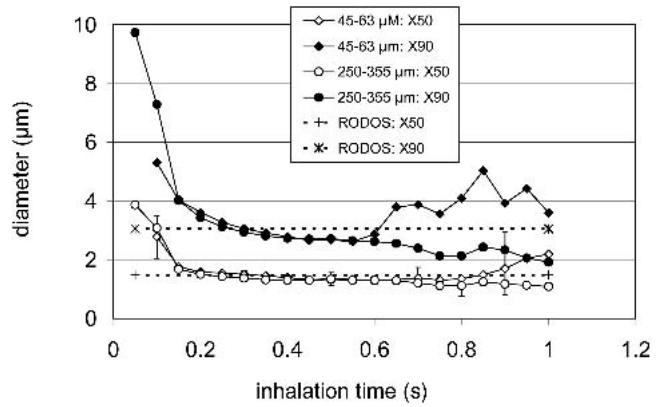

Fig. 6. X_{50}- and X_{90}-values from the cumulative size distribution curves for the aerosol from the classifier (at 60 l/min) as function of the inhalation time. Mixtures with carrier size fractions 45–63 and 250–355 μm and 4% budesonide. X_{50}- and X_{90}-values from RODOS dispersion (5 bar) are given for comparison with the primary particle size distribution of the drug. Spread bars (only for the X_{50}-values in the aerosols) indicate the maximal and minimal values obtained for five doses.

much lower drug detachment rate. This has the consequence that a rather long inhalation time is necessary to yield a size distribution in the entire inhaled aerosol that is representative for the primary particle size distribution of the drug.

The rather exclusive release of the largest drug particles (agglomerates) within the first 0.1 to 0.2 s confirms that these particles are not only attached with the highest adhesive forces but also subjected to the highest inertial removal forces. This supports a previously presented force distribution concept (5), which can be used to explain the dramatic drop in release rate constant (k) after 0.5 s of circulation in the classifier. Figure 8 is an improved presentation of this concept, which is a model used to explain the consequences of changes in the size distributions of removal and adhesive
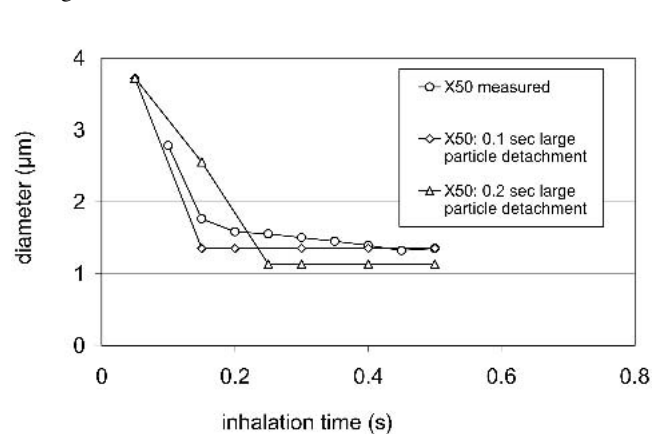

Fig. 7. X_{50}-value of the aerosol from the classifier (at 60 l/min) as function of the inhalation time for carrier fraction 45–63 μm with 4% budesonide (circles) in comparison with computed changes in X_{50}. For the computations, it has been assumed that exclusively the largest particles are removed in the first 0.1 (squares) and 0.2 s of circulation (triangles), respectively, and that remaining drug particles are next detached randomly (yielding a constant X_{50}-value in the aerosol). Computations have been based on size distributions for the drug obtained from RODOS measurement at 5 bar. Detached fractions within the first 0.1 and 0.2 s have been calculated with rate constants depicted in Fig. 1.
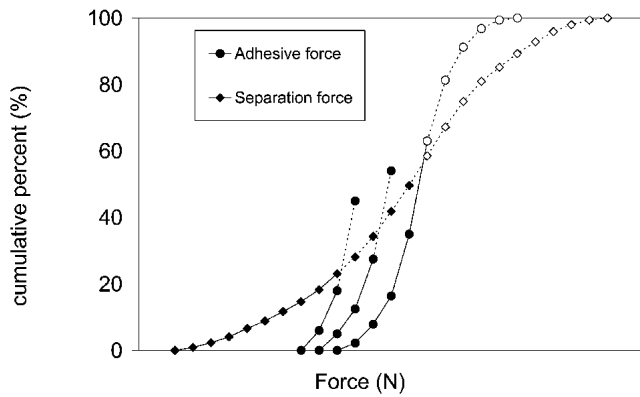
Fig. 8. Force distribution concept showing the cumulative size distributions of adhesive forces (in the mixture) and removal forces (during inhalation) relative to each other for a stationary flow situation. The intersections of both curves derived from carrier residue measurements are for the situations after 0.5, 3, and 6 s circulation in a classifier, respectively. Further explanation: see text.

forces. From the proportionalities ($F_R \propto d^3$ and $F_A \propto d^1$) between both forces and the drug particle diameter (known from laser diffraction analysis), it may be expected that the size distribution of the removal forces is wider than that of the adhesive forces. As explained before (1,5,9), the span of the ranges may be influenced by drug particle agglomeration (increasing particularly F_R), the action of press-on forces during mixing and the presence of active sites. Therefore, the absolute numerical values for the adhesive forces cannot precisely be given. They are not necessary for the explanation, however, as only the position of the size distributions of both forces relative to each other is important. This determines the intersection of both curves for which the carrier residue is a good measure. Figure 8 shows the distributions for adhesive (circles) and removal forces (squares) for a stationary circulation velocity in the classifier. It must be expected that when the stationary situation is achieved (e.g., after 0.5 s in Fig. 8), all particles for which $F_R > F_A$ are already dislodged. Adhesive and removal forces of detached particles do no longer exist, which is the reason why they are depicted with open symbols. For the drug particles that are still attached to the carrier crystals after 0.5 s of circulation, the ratio of F_R to F_A is smaller than 1. Hence, further detachment is only possible when the adhesive forces are weakened during circulation by repeated carrier particle collision. From previous investigations with adhesive mixtures it is well known that drug particle detachment from carrier surfaces under stationary shear and impact conditions increases with time (3,11). Weakening is expected to occur particularly when the inertial forces act in various directions on the same adhering particle, as during circulation in a classifier. The shift in adhesive forces for remaining particles by weakening decreases the intersection between both distribution curves to lower values as shown in Fig. 8 for 3 and 6 s of circulation in the classifier. The magnitude of the shift can again be derived from the carrier residue. The rate with which the intersection shifts due to weakening is relatively low and so will be the drug release rate for t > 0.5 s.

CONCLUSIONS

The mode of drug particle detachment from carrier crystals during inhalation of adhesive mixtures with an air classi-

fier–based inhaler may be as a mixture of primary particles and small agglomerates, depending on the carrier size fraction, payload, and, particularly, the flow rate during inhalation. Our results strongly suggest that two different types of drug agglomerates exist. So-called natural agglomerates that are present in the starting material may not completely be disintegrated during mixing nor during inhalation after dislodgement from the carrier crystals. Agglomerates formed on the carrier surface from primary drug particles by the action of press-on forces during mixing are much weaker. They already disintegrate at relatively low de-agglomeration forces (30 l/min in the classifier used for this study). The size of the detached agglomerates of the second type increases with the carrier payload. This seems to support the hypothesis of Louey and Stewart (4) that the presence of multilayer associations may allow greater drug detachment from the carrier surface due to the increased detachment mass. However, this is only true for fine carrier fractions as the press-on forces not only increase the size of the agglomerates, but also the size of the adhesive forces between the agglomerates and the carrier surface. This increases the fraction of drug not detached from the carrier with increasing mean carrier diameter for the same drug payload (9). The results confirm that carrier residues, although very relevant to studying the drug-to-carrier interaction as function of various parameters, cannot be used unconditionally to predict the fine particle fraction (e.g., 1,5,9). Detached particles may not be fully de-agglomerated into primary entities before they are discharged from the classifier, whereas the size of detached particles may also vary with the inhalation time.

It has been shown that predominantly the largest particles (and agglomerates) are dislodged during the first phase of inhalation, which confirms that the largest particles are subjected to the highest removal forces. It seems plausible that a high rate of detachment is confined to the fraction of drug particles for which the ratio of F_R to F_A is > 1 in the stationary flow situation through the classifier, which situation is normally achieved within the first 0.5 s of inhalation. A much slower rate of detachment for smaller particles after approximately 0.5 s could be the consequence of weakening of the adhesive forces (from repeated carrier particle collision) or wear of the surface of the carrier crystals during circulation in the classifier.

REFERENCES

1. A. H. de Boer, P. Hagedoorn, D. Gjaltema, D. Lambregts, J. Goede, and H. W. Frijlink. The rate of drug particle detachment from carrier crystals in an ordinary air classifier–based inhaler. *Pharm. Res.* **21**:2158–2166 (2004).

2. P. Kulvanich and P. J. Stewart. The effect of particle size and concentration on the adhesive characteristics of a model drug-carrier interactive system. *J. Pharm. Pharmacol.* **39**:673–678 (1987).

3. K. Iida, Y. Hayakawa, H. Okamoto, K. Danjo, and H. Leuenberger. Preparation of dry powder inhalation by surface treat-

ment of lactose carrier particles. *Chem. Pharm. Bull.* **51**:1–5 (2003).

4. M. D. Louey and P. J. Stewart. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. *Pharm. Res.* **19**:1524–1531 (2002).

5. A. H. de Boer, P. Hagedoorn, D. Gjaltema, J. Goede, and H. W. Frijlink. 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. *Int. J. Pharm.* **260**:187–200 (2003).

6. M. J. Clarke, J. Peart, S. Cagnani, and P. R. Byron. Adhesion of powders for inhalation: an evaluation of drug detachment from surfaces following deposition from aerosol streams. *Pharm. Res.* **19**:322–329 (2002).

7. B. H. J. Dickhoff, M. J. H. Ellison, A. H. de Boer, and H. W. Frijlink. 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 (2002).

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

9. B. H. J. Dickhoff, A. H. de Boer, D. Lambregts, and H. W. Frijlink. The effect of carrier surface and bulk properties on drug particle detachment from crystalline lactose carrier particles during inhalation, as function of carrier payload and mixing time. *Eur. J. Pharm. Biopharm.* **56**:291–302 (2003).

10. A. H. de Boer, P. Hagedoorn, D. Gjaltema, J. Goede, and H. W. Frijlink. Air classifier technology (ACT) in dry powder inhalation part 2. The effect of lactose carrier surface properties on the drug-to-carrier interaction in adhesive mixtures for inhalation. *Int. J. Pharm.* **260**:201–216 (2003).

11. J. N. Staniforth and J. E. Rees. Effect of vibration time, frequency and acceleration on drug content uniformity. *J. Pharm. Pharmacol.* **34**:700–706 (1982).