Chapter 6

The rate of drug particle detachment from carrier crystals in an air classifier based dry powder inhaler

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Abstract

In this chapter, the rate with which drug particles are detached from carrier particles in adhesive mixtures when the action of the separation forces during inhalation is sustained by circulation of the powder dose in an air classifier has been studied. Residual drug on retained carrier particles from different adhesive mixture compositions has been analysed after different circulation times in the classifier (varying from 0.5 to 6 s) at two different flow rates. For calculation of the detachment rate within the first 0.5 s of inhalation, the optical concentration of the aerosol from the classifier has been measured with laser diffraction technique. It was found that the detachment rate varies with the carrier size fraction and carrier payload and the rate is clearly highest within the first 0.5 s of inhalation for all fractions at all payloads. By modelling of the rate of drug detachment from the carrier crystals, it could be shown that detachment approaches first order reaction kinetics within the first half second of inhalation. But at longer circulation times in the classifier, the de detachment rate decreases dramatically. This most likely is the result of a decreasing ratio of removal forces to adhesive forces. To increase the detached fraction of drug during inhalation at a constant flow rate, a short residence time for the powder in the de-agglomeration principle between 0.5 and 2 s is desired.

Keywords: Adhesive mixtures, Air classifier, Carrier residue, Dry powder inhaler with residence time, Particle detachment rate

1. Introduction

Particles for respiratory drug delivery have to be in the approximate aerodynamic size range between 1 and 5 μm. Generally, such particles for dry powder inhalation are processed into a free-flowing formulation to improve handling and dose consistency. The efficacy of dry powder inhalers (dpi's) depends on the extent to which the primary drug particles in the formulation can be dispersed into a suitable aerosol during inhalation. When the formulation is an adhesive mixture, this refers to the mass fraction of drug particles in a single dose that can be detached from the carrier crystals in the mixture. Different studies are known in which the type and size of the adhesive forces between drug and carrier particles in adhesive mixtures for inhalation are described (e.g. Visser, 1989; Li et al., 1996; Zang and Whiten, 1996; Podczeck, 1996, 1998a). Many parameters have been investigated that influence the size of these forces, like for instance the carrier payload (Steckel and Müller, 1997a; Dickhoff et al., 2003), the mixing time (Zeng et al., 2000a; Dickhoff et al., 2003), the relative humidity (Maggi et al., 1999; Price et al., 2002), tribocharge (Carter et al., 1992; Schönert et al., 1996), carrier type and grade (Podczeck, 1998b; Larhrib et al., 1999; Harjunen et al., 2002; Louey et al., 2003) and more in particular the carrier surface morphology (Kawashima et al., 1988; Zeng et al., 2000b). Modification of the carrier smoothness and purity has been explored to reduce the drug-to-carrier interaction force, thereby enhancing drug re-dispersion during inhalation (Zeng et al., 2001a/b; Young et al., 2002; Iida, 2003). It is also well known that the size of the adhesive force between a drug and carrier particle is increased by increasing the pressure with which the drug particle is attached (Lam and Newton, 1992; Podczeck, 1996). It has recently been shown that the carrier bulk properties during mixing are thus important in this respect (Dickhoff et al., 2003). Collisions between crystals during mixing may result in firm pressing of the drug particles against the carrier surfaces, thereby increasing the adhesive forces between the both.

Also relevant to the fine particle mass fraction (fpf) obtained during inhalation with breath controlled dpi's are the type and size distribution of the separation forces into which the kinetic energy of the airflow is transformed. It has been shown that an increase in kinetic energy results in an increase in the fpf (Chew et al., 2002). Also generating a more efficient type of separation force may yield a higher fpf (Steckel and Müller, 1997b; de Boer et al., 2003a). Therefore, achieving a high fine particle fraction requires not only optimising the adhesive forces in the mixture, but also proper balancing between the adhesive and the removal forces during inhalation. Sustaining the action of the removal forces during a part of the inhalation time is another possibility to increase the fraction of drug particles released from the carrier crystals (de Boer et al., 2003a). Sustained action can for instance be realised with an air classifier that has the ability to retain large carrier particles and to release only the small drug particles. Because the carrier circulation (residence) time in a classifier is finite and has to comply with patients' inspiratory abilities and regulatory requirements, optimisation between classifier design (residence time) and formulation (drug detachment rate) is necessary. Considering the recommendations that the total dose is inhaled in 2 l, a residence time between 0.5 and 1.5 s seems preferable.

The aim of this study is to investigate the rate of drug particle detachment from carrier crystals in an air classifier as function of carrier size fraction, carrier payload and inspiratory flow rate, using a previously described technique of analyzing residual drug on retained carrier (carrier residue: CR) after inhalation (de Boer et al., 2003a). To obtain more detailed information about the release rate within the first 0.5 s of inhalation, the optical concentration of the aerosol from the classifier has been measured with laser diffraction technique. Furthermore, a mathematical exercise was undertaken to gain better understanding of the processes that determine the release rate of the drug from the carrier. Because the detached drug fraction (100 - CR) is not necessarily representative for the obtained fine particle

fraction, also the mode of drug particle detachment has been investigated, which will be reported in Chapter 7.

2. Materials and methods

2.1. Materials

Alpha lactose monohydrate carrier fractions of various size ranges were obtained by 20 min vibratory sieving (Analysette 3, Fritsch, Idar-Oberstein, Germany) followed by 10 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). Micronised budesonide with an X_{50} of 1.04 μm (X_{10} = 0.54; X_{90} = 2.15 μm) from laser diffraction analysis (RODOS dispersion at 5 bar) was supplied by Sofotec (Frankfurt, Germany).

2.2. Adhesive mixture preparation and characterisation

Adhesive mixtures with different budesonide concentrations (% w/w) and different carrier size fractions were prepared in a stainless steel mixing container of 160 x 10^{-4} m^3, using a tumbling mixer (Turbula T2C, WA Bachofen, Basel, Switzerland) at 90 rpm. Batch size was 25 g and mixing times were 10, 60, 120 and 240 min respectively. The budesonide was screened through a 90 micron sieve prior to mixing in order to break up the larger agglomerates in the powder. Mixture homogeneity was determined on 20 samples of 25 mg each. The samples were dissolved in 20 ml of ethanol p.a., separated from non-dissolved 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.

2.3. Carrier residue measurements

Inhalation experiments were performed with an air classifier based test inhaler of which the working principle and the procedures for use have been described previously (de Boer et al., 2003a). For the carrier residue experiments, the test inhaler was connected to an impactor of the Fisons type of which the third (instead of the fourth) stage was connected to 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 flow rate through the inhaler is established. The inhalation manoeuvre through the inhaler was controlled with a previously adjusted flow controller and a solenoid valve connected to a timer. After each inhalation, retained carrier particles were removed from the classifier and analysed for residual drug, using the same procedures as described for homogeneity testing of the mixtures. Each data point in the Figs. 6.1, 6.2 and 6.5 is the mean of two duplicate series of five inhalations of 25 mg each.

2.4. Laser diffraction experiments

For the laser diffraction experiments, a HELOS BF-MAGIC with standard Windox software (Fraunhofer calculation) was used (Sympatec, Clausthal-Zellerfeld, Germany). All measurements were performed with a 100 mm lens. For optical concentration (C_{opt}) measurements in the aerosol from the test inhaler (the same as used for the carrier experiments), a previously described inhaler adapter (with minor counter flow) was applied (de Boer et al., 2003b). All C_{opt}-data given are the mean of three inhalations (25 mg). Start of the measurements was synchronised with opening of the solenoid valve to start a previously adjusted flow rate through the inhaler. Total measuring time per inhalation was 1 s, and each measurement was sliced into intervals of 20 ms, yielding 50 data points per inhalation. Flow

adjustment and reference measurements were conducted with the same amount (25 mg) of carrier fraction (no drug) inside the classifier for correction of detached lactose fines.

2.5. Calculations

Percent carrier residue (CR) is the ratio of residual carrier payload (% drug w/w) after inhalation to initial payload multiplied by 100, corrected for a minor carrier discharge from the classifier.

Percent carrier coverage (CC) is the carrier surface payload (mg/m^2) as percent of a monolayer of drug particles around the carrier crystals. For calculation of a monolayer of drug particles, it was assumed that all drug particles are spherical and monodisperse (diameter equals the median diameter from laser diffraction analysis using RODOS dispersion). 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 spherical particle and that there is no space between the squares.

To compare the results from laser diffraction with those from carrier residue measurement, the area under the curve for the optical concentration as function of inhalation time has been calculated for each time interval (0.02 s) between 0 and 0.5 s of inhalation:

$$AUC_{t1\text{-}t2} = 0.02 \text{ x } (C_{opt,t1} + C_{opt,t2})/2 \qquad [6.1]$$

The interval-values $AUC_{t1\text{-}t2}$ were processed into a cumulative curve as function of inhalation time. Each interval value was next expressed as percent of the cumulative sum, which is given by Eq. 6.2:

$$(AUC_{TOT} = \Sigma\, AUC_{t1\text{-}t2}) \qquad [6.2]$$

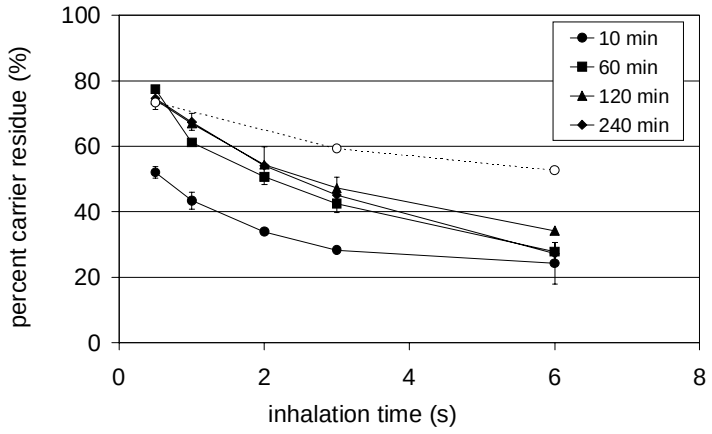
The sum has been equated with the detached fraction (100 - CR) from carrier residue measurements within the same time interval (0 - 0.5 s) for the same formulation (at the same flow rate). From this, the (cumulative) detached fraction within the first half second of inhalation could be assessed after each time interval, after it was checked that changes in size distribution of the aerosol within this time period do not influence the computations too much.

3. Results and discussion

3.1. The rate of drug particle detachment experimentally

The percent carrier residue (CR) at 60 l/min (closed symbols) as function of inhalation time is presented in Figs. 6.1A-B for 0.4% mixtures and in Figs. 6.2A-B for 4% mixtures, for four different mixing times. In this study, a fine (45-63 μm; Figs. 6.1A and 6.2A) and an intermediate (150-200 μm; Figs. 6.1B and 6.2B) carrier fraction have been investigated. For the mixtures prepared at ten minutes mixing time, also the decrease of CR at 30 l/min (open symbols) is shown. Because the effects obtained from increasing the mixing time were basically of the same type at both flow rates, as well as for clarity of the figures, CR data for other mixing times at 30 l/min are not presented. A relevant conclusion from Figs. 6.1 and 6.2 is that doubling the time during which the separation forces act within the first half second of inhalation, can cause approximately the same decrease in CR as doubling the flow rate (CR = 100 for t = 0). After the first 0.5 s of inhalation, the effect of flow rate becomes greater than that of time. This observation is important for classifier design, particularly when establishing the residence time for the powder.

A



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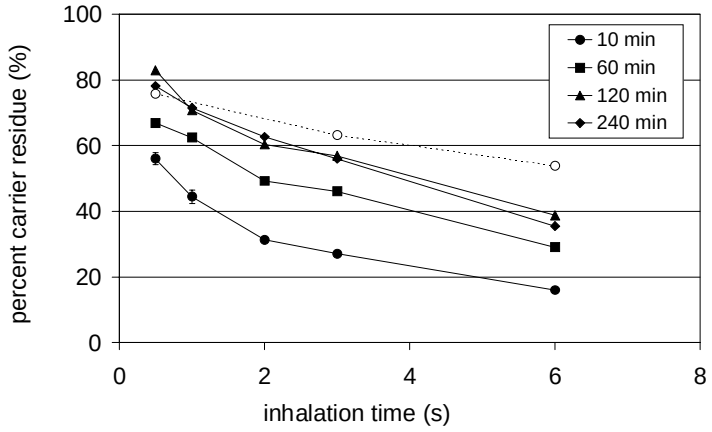
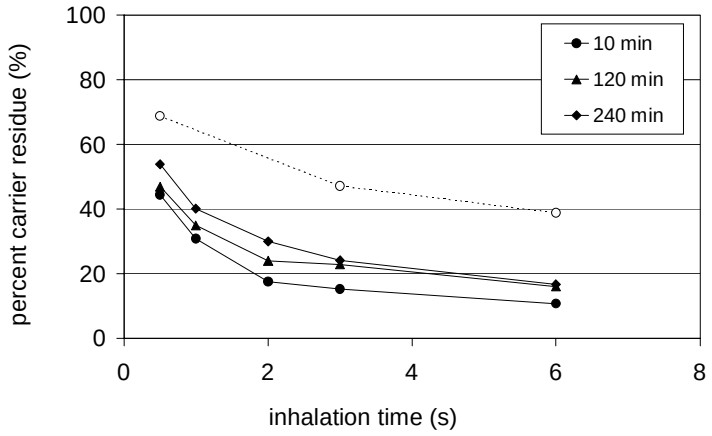


Figure 6.1. Carrier residue (as percent of initial payload) as function of the inhalation time for 0.4% budesonide mixtures at four different mixing times. Carrier size fractions 45-63 µm (A) and 150-200 µm (B). Open symbols refer to 30 l/min; closed to 60 l/min. The carrier residues at 30 l/min are for the 10 min mixture. The spread bars (given for the 10 and 240 min mixtures only) indicate the spread between the two duplicate series (of five inhalations each).

The results in Figs. 6.1 and 6.2 are in good agreement with previously presented data obtained at a fixed inhalation time of 3 s (Dickhoff et al., 2003). Mixtures of both carrier fractions yield much lower carrier residues at 4% than at 0.4% payload (compared at the same inhalation time). At a flow rate of 60 l/min, the separation forces are relatively high compared to the adhesive forces and only the strongest bonds in the mixture can not be overcome at inhalation times of 6 s and more (Dickhoff et al., 2003; de Boer et al., 2003a). When the carrier payload is increased (from 0.4 to 4% w/w), the number of drug particles relative to the number of sites with high adhesive forces (‘active sites’ on the carrier surface) increases. A higher ratio of the number of drug particles to the sites with high binding forces is also the reason why mixtures with 4% payload are less sensitive to increasing the mixing time than 0.4% mixtures. At higher payloads, most active sites are already occupied within the first 10 min of mixing time. At lower payloads, the powders produced by short mixing times exhibit a random distribution of drug particles over carrier sites with high and those with low binding forces. Increased mixing times shift the distribution towards the sites with higher binding forces (Dickhoff et al., 2003).

A



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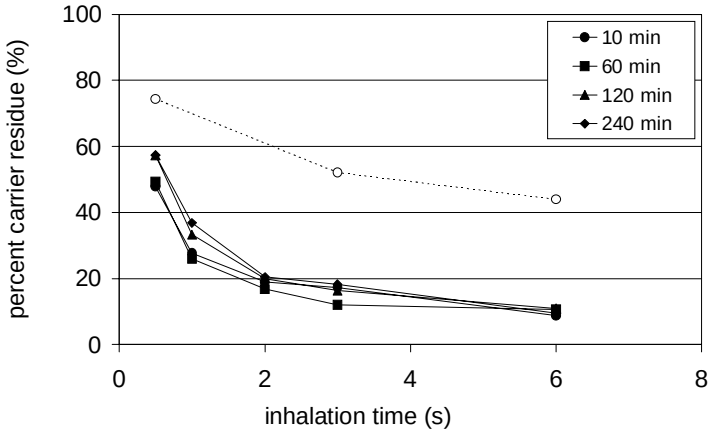

Figure 6.2. Carrier residue (as percent of initial payload) as function of the inhalation time for 4% budesonide mixtures at three (A: 45-63 μm), respectively four (B: 150-200 μm) different mixing times. Open symbols refer to 30 l/min; closed to 60 l/min. Variation is of the same order of magnitude as shown in Figs. 6.1A and B.

The explanations are supported by scanning electron micrographs. Figs. 6.3A and B show that most drug particles are in the carrier surface cavities and irregularities at 0.4% payload. The arrow in Fig. 6.3A indicates one of the many examples that can be seen on this micrograph. In such irregularities the potential for high adhesive forces is relatively high (de Boer et al., 2003c). On the other hand, irregularities can also provide shelter from press on forces during the mixing process (Dickhoff et al., 3002). Figs. 6.3C and D depict mixtures with 4% payload. As an example, Fig. 6.4 shows the carrier residues for the mixture with carrier fraction 150-200 μm at 4% payload after 0.5 (A) and 6 (B) s of inhalation respectively, at 60 l/min. In the first phase of inhalation (approximately 0.5 to 1 s), predominantly the largest drug particles and those attached to smooth carrier crystal planes are removed. Apparently, detachment of smaller drug particles, or those deposited in the carrier surface cavities and irregularities, where the adhesive forces are generally higher, requires sustained carrier particle circulation in the classifier to obtain a separation force in the desired direction or to weaken existing adhesive forces (de Boer et al., 2003a).

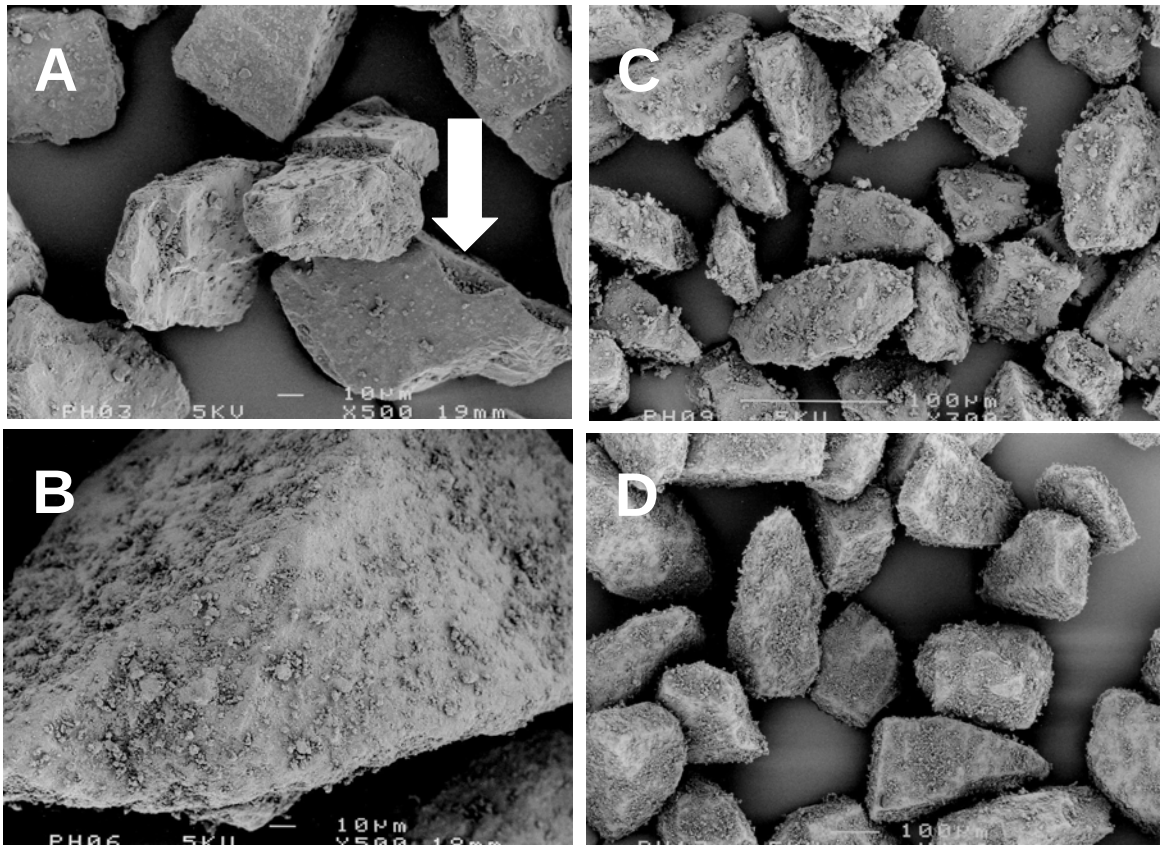

Figure 6.3. Scanning electron micrographs of mixtures prepared at 10 min mixing time. A: carrier size fraction 45-63 µm with 0.4% (w/w) budesonide (microscopic magnification is 500x); B: fraction 150-200 µm with 0.4% budesonide (500x); C: fraction 45-63 µm with 4% budesonide (300x); D: fraction 150-200 µm with 4% budesonide (100x). Magnifications for the 4% mixtures have been selected differently to show approximately the same number of carrier particles. The arrow in Fig. 3A indicates an example of drug particles accumulated in carrier surface discontinuities.

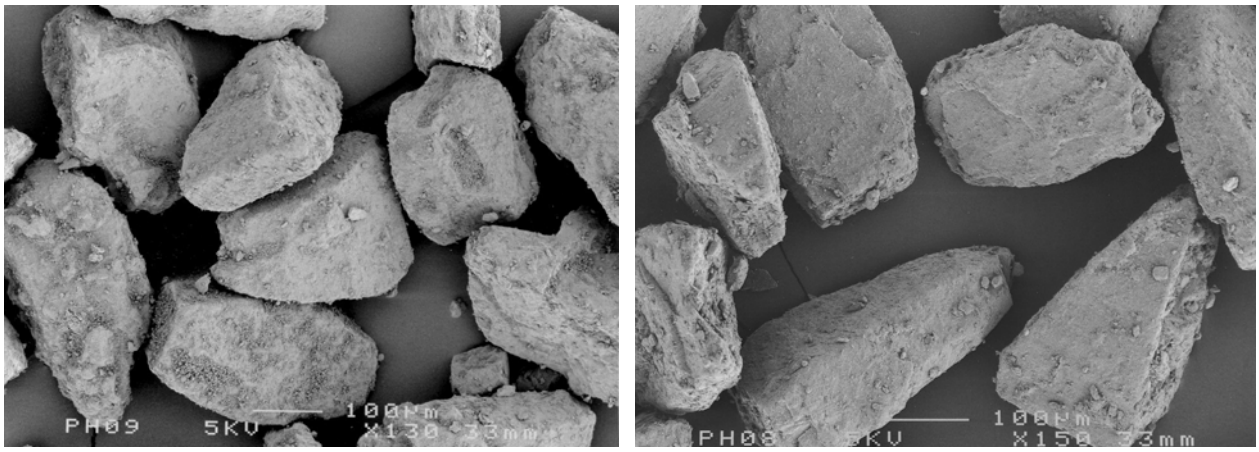

Figure 6.4. Scanning electron micrographs of retained carrier particles from the (10 min) mixture with carrier size fraction 150-200 µm and 4% (w/w) budesonide after inhalation at 60 l/min for 0.5 (left) and 6 s (right).

3.2. Modelling of the rate of drug particle detachment

The exponential decrease in CR with the circulation time for all mixtures at all mixing times and at both flow rates, gives the impression that the rate of change in CR is proportional to the actual carrier residue at any given moment. This has similarity with a first order process, which is described by the equation:

$$- dCR/dt = k.CR \qquad [6.3]$$

where k is the rate constant.

Actually, CR is not the correct parameter in this respect. Being a relative measure, it does not discriminate between absolute carrier payloads (% drug w/w). Nor does it take account of differences in specific surface area between different carrier size fractions. As a result, the same weight concentration of drug in the mixture may yield a wide range of values for the surface payload (CSP in mg drug per m^2), which is the real drug concentration ('reactant') to follow as function of the inhalation time. For this reason, carrier residue (CR) has been substituted by carrier surface payload (CSP):

$$-dCSP/dt = k.CSP \qquad [6.3a]$$

After rearrangement of the terms and integration, (6.3a) yields the expression:

$$\ln CSP = -k.t + C, \qquad [6.3b]$$

where C is a constant.
When t = 0, CSP equals the initial surface payload CSP_0 and C becomes $\ln CSP_0$.
So, equation (6.3b) may be written as:

$$\ln CSP = -k.t + \ln CSP_0$$

Another rearrangement of terms yields the expression:

$$k.t = \ln CSP_0 - \ln CSP = \ln (CSP_0/CSP), \text{ so}$$

$$k = \{\ln (CSP_0/CSP)\}/t \qquad [6.4]$$

When the drug release rate (-dCSP/dt) follows first order kinetics, k in Equation 6.4 is a constant. Similarly as the temperature determines the rate constant of a chemical reaction, k in the process of drug particle detachment from carrier crystals during inhalation varies with the inspiratory flow rate. Because the flow rate determines the removal force F_R, it is plausible to assume that the constant k is a function of the ratio of the removal forces (F_R) to the adhesive forces (F_A) which constitute the resistance against detachment.

Fig. 6.5 seems to confirm that the initial drug particle detachment (first 0.5 s) approaches first order kinetics. In this figure, the release rate constant in the first half second of inhalation ($k_{0.5}$) is presented as function of the percent carrier coverage (CC) for the mixtures in the Figs. 6.1 and 6.2 with 10 min mixing time. It appears that in spite of a tenfold increase in CC, $k_{0.5}$ increases less than 30% (for the same carrier fraction at the same flow rate). The reason for presenting $k_{0.5}$ as function of percent carrier coverage, is because CC expresses the extent of carrier surface occupation by drug particles more explicitly than the surface payload (CSP in g/m^2). CC clearly discriminates between monolayer (CC <100%) and

multilayer (CC >100%) coverage, which information can not be derived from the numerical value of the carrier surface payload.

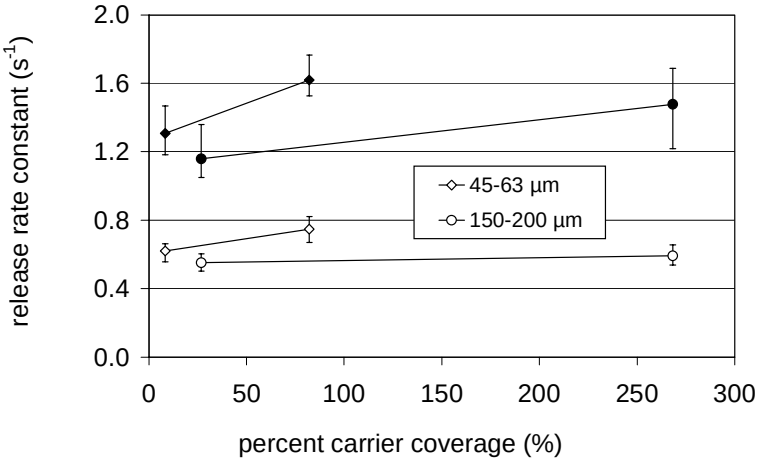

Figure 6.5. Release rate constant within the first half second of inhalation ($k_{0.5}$) as function of percent carrier coverage (CC as percent of a theoretical monolayer of drug particles) for the mixtures in Figs. 6.1 and 6.2 (10 min mixing time). Open symbols refer to data obtained at 30 l/min; closed to those at 60 l/min. Data points are linked for the same carrier fraction with two different carrier payloads. Spread bars indicate the maximal and minimal values obtained for n = 10.

3.3. Proposal of possible detachment mechanisms

When the release rate constant (k) for longer inhalation times (same mixtures) is plotted against the percent carrier coverage, a steep decrease of k with increasing inhalation time is obtained (Fig. 6.6). In Fig. 6.6, k-values are linked for a series of subsequent inhalation times per mixture (and per flow rate).

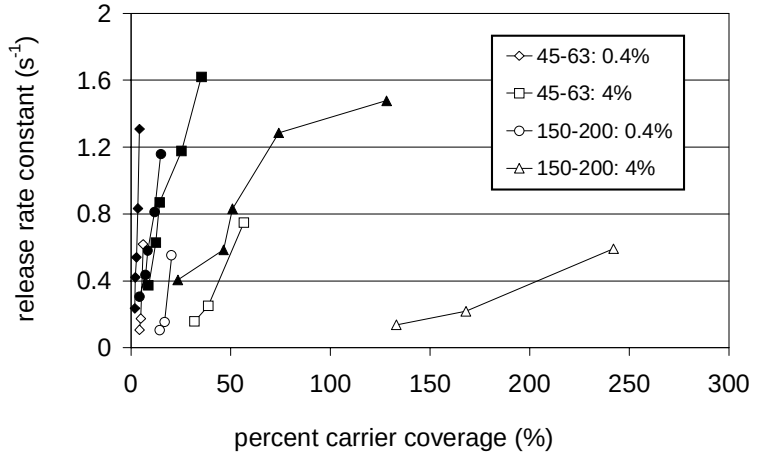

Figure 6.6. Release rate constant (k) as function of percent carrier coverage (CC as percent of a monolayer of drug particles) for the mixtures in Figs. 6.1 and 6.2 (10 min mixing time). Open symbols refer to data obtained at 30 l/min; closed to those at 60 l/min. Data points obtained at different inhalation times are linked for the same mixture. Open symbols refer to data obtained at 30 l/min; closed to data obtained at 60 l/min. Each data point is the mean of two series of five inhalations each. Spread bars: see Fig. 6.5.

The decrease in k with time in Fig. 6.6 suggests that, in addition to the carrier surface payload (drug concentration) another variable parameter becomes involved in the drug particle detachment from carrier crystals at prolonged inhalation times (at a constant flow rate). Since k is a function of the ratio of F_R to F_A, it could either be that F_R decreases, or that F_A increases with increasing amount of drug particles dislodged, or both. A decreasing F_R at a constant inspiratory flow rate occurs only when the mass of subsequently detached particles becomes less, e.g. when large primary particles and/or agglomerates are dislodged first and smaller primary particles next. This may be possible, because it has been described that drug particles tend to form particle agglomerates on the carrier crystals, even at drug concentrations well below that for a monolayer on the carrier surface (Kulvanich and Stewart, 1987). An increasing F_A with increasing number of particles already separated from the carrier could have different reasons, depending on the initial carrier payload and the size and effectiveness of press-on forces during the mixing process (Dickhoff et al., 2003). For the mixtures in Fig. 6.6, the initial carrier coverage varies from 8.2% (for the carrier size fraction 45-63 µm with 0.4% budesonide) to 268.3% (for the fraction 150-200 µm with 4% drug). The particle-particle attraction within this range of mixtures may cover a wide size range of cohesive and adhesive forces, the first occurring particularly at high carrier payloads (drug-to-drug interactions); the latter at all payloads between drug and carrier particles. Therefore, drug particle detachment during inhalation could theoretically also comprise different phases. The break-up of mainly cohesive forces during the first phase of inhalation when CC is still larger than 100% could occur as the first step. Subsequently, when CC decreases to values < 100%, primarily weak adhesive forces between drug particles and smooth carrier surfaces are the target. Which leaves the highest adhesive forces to remain at lower surface payloads, in a phase during which most drug particles still attached to the carrier are located on most active binding sites. This peeling off layer by layer would basically be a different mode of detachment than that in which the higher particle masses (e.g. agglomerates) are dislodged first and the smaller ones next. Starting at a much lower carrier payload (CC << 100%), also sequencing of particle detachment may occur. Large particles and particles attached to smooth carrier surfaces may be dislodged first and those in the surface irregularities next.

3.4. Discussion of proposed detachment mechanisms

Fig. 6.6 shows that each mixture has its own relationship between the detachment rate constant and the percent carrier coverage. The observation that the initial rate constant values are much higher at 60 than at 30 l/min, seems to prove that k is a function of F_R/F_A. The rate constant at any moment from the start of inhalation has approximately the same value for all mixtures with the same carrier fraction, in spite of the extreme differences in CC. This makes the peel-off mechanism (layer by layer) without further adjustment of the theory unlikely, because it suggests that the size of the interaction forces in the mixture is not solely determined by the type of force (cohesive, or weak and strong adhesive forces). If this were true, k would have to be high at a high carrier coverage for all mixtures and change first significantly when the phase of breaking primarily cohesive forces passes on to the phase of breaking adhesive forces between drug and carrier. The fact that k decreases rather with the inhalation time than with the percent carrier coverage, indicates that peeling off in layers is a strong simplification of the real situation. A better explanation may be obtained from taking the action of press-on forces into consideration. Such inertial and frictional press-on forces occur when carrier particles collide with each other, or when they are displaced relative to each other during the mixing process (Dickhoff et al., 2003). They increase the adhesive and cohesive forces in the mixture and are for instance responsible for the previously mentioned drug particle agglomeration on the carrier surface (Kulvanich and Stewart, 1987). Particles attached to smooth carrier surfaces are generally within reach of such forces. Consequently,

drug particles may be attached firmly to smooth crystal planes, in spite of the fact that such crystal planes are not considered as sites with a high bonding potential. These crystal planes can therefore be considered as pseudo-active sites. Particles in surface discontinuities find shelter from press-on forces at lower carrier payloads. However, at higher (multi-particular) surface payloads, impact forces can be transferred from outer particle layers to particles which are in direct contact with the carrier surface. Under these circumstances, adhesive forces between the drug and carrier particles can even be increased on places where press-on forces are not effective when the carrier payload is low. Such circumstances are for instance achieved in the case of a mixture with carrier size fraction 150-200 μm and a carrier payload of 4% budesonide (268.3% carrier coverage).

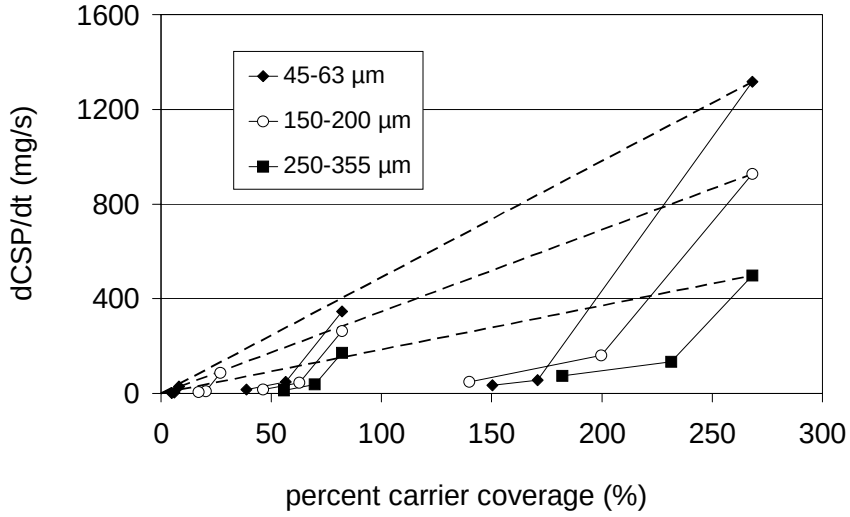

Figure 6.7. Detachment rate (dCSP/dt) at 30 l/min as function of percent carrier coverage for carrier size fractions 45-63 and 150-200 μm with 0.4 and 4% drug from Fig. 6.6, and some additional mixtures: 10 min mixing time. The drug concentrations of the additional mixtures have been chosen such that the same degrees of initial carrier coverage were obtained (CC as percent of a monolayer of drug particles is 82.2% or 268.3%). Data points obtained at different inhalation times are linked for the same mixture to show the dramatic decrease in detachment rate with increasing inhalation time. Dotted lines indicate first order release rate. Each data point is the mean of two series of five inhalations each. Spread bars: see Fig. 6.5.

In Fig. 6.6 only one mixture has an initial carrier coverage of more than 100%. To find more support for the hypothesis that the press-on forces during the mixing process influence the release rate constant, some additional mixtures with higher CC were prepared. The results are presented in Fig. 6.7 for different investigated time intervals during inhalation at 30 l/min. The experiments have been confined to this lower flow rate at which the effects are most pronounced. The release rates have been presented as function of the percent carrier coverage at the start of each time interval and linked for subsequent inhalation times of the same mixture. The mixtures 45-63 and 150-200 μm with 0.4 and 4% budesonide in this figure are the same as in Fig. 6.6. Carrier payloads of the additional mixtures were selected to obtain the same degree of initial carrier coverage of 82.2 and 268.3%, corresponding with 4% (w/w) drug on carrier fraction 45-63 μm and 150-200 μm respectively. According to first order kinetics (- dCSP/dt = K.CC, Equation 6.3a, where K includes a conversion factor for CSP into %CC), dCSP/dt (per m^2) has to decrease with decreasing percent carrier coverage as indicated

with the dotted lines (when having CC = 268.3% as starting point). The lines are different for the different carrier fractions. Indeed, the detachment rate within the first half second of inhalation decreases along the predicted lines. However, when the de-agglomeration is sustained over longer inhalation times (3, respectively 6 s), dCSP/dt appears to deviate quite rapidly from these lines. The rate with which dCSP/dt deviates from first order seems to be widely independent of the carrier fraction and the residual carrier coverage. This leaves two different effects to explain: a decrease in initial release rate with increasing carrier diameter (different dotted lines) and a much stronger decrease in release rate than expected (on the basis of first order kinetics) with increasing inhalation time.

Apparently, a certain fraction of the initial amount of drug can easily be detached, whereas another fraction can not. The size of the fraction not detached at 30 l/min has no clear relationship with the number of active sites for the range of investigated carrier payloads (0.4 to 13% w/w). Particularly at the higher carrier surface payloads (CC > 100%), these sites have become completely saturated. There is a relationship between the detachment rate and the carrier diameter however, as shown in Fig. 6.7. This relationship leads to the conclusion that at least a part of the particle-particle interaction forces during mixing is increased by carrier particle collisions. Obviously, these collisions result in the highest press-on forces for the largest carrier particles, having highest mass and the best flow properties. This effect of size occurs next to that of the duration of these forces, as can be observed when the mixing time is increased (Figs. 6.1 and 6.2). The ratio of F_R to F_A for the firmly adhering drug particles is not changed to the extreme by the press-on forces however, as doubling the flow rate (from 30 to 60 l/min) has the consequence that the residual fraction can be diminished to only 10 to 20% (Figs. 6.1 and 6.2).

A conclusive explanation for the extreme decrease of k after 0.5 s of inhalation in a classifier can not be given yet. As discussed, it is not necessary that the drug particles within the easily removed fraction are associated with lower adhesive forces. It could also be that this fraction consists primarily of small agglomerates with a relatively high removal force (F_R) during inhalation. From laser diffraction analysis of the aerosol cloud from the classifier, it is known that the size of the dislodged particles increases with increasing mean carrier diameter, as shown in Table 6.1 for mixtures with 4% (w/w) drug.

Table 6.1. Size distribution of particles in the aerosol cloud from the classifier at 10 l/min obtained with laser diffraction analysis for mixtures with different carrier size fractions and 4% (w/w) of drug in comparison with the size distribution of the drug from RODOS dispersion at 5 bar (n = 5).

	X_{10} (μm)	X_{50} (μm)	X_{90} (μm)
Drug (RODOS)	0.54	1.04	2.15
Mixture with carrier fraction 45-63 μm	1.21	2.26	3.75
Mixture with carrier fraction 150-200 μm	1.39	2.90	9.76
Mixture with carrier fraction 250-355 μm	1.76	4.75	24.68

Because the X_{90}-values in the aerosol (at 10 l/min) exceed that for the primary drug particles from RODOS dispersion, detachment of agglomerates must be involved. According to this, one would expect that the detachment rate within the first half second of inhalation (Fig. 6.7) increases with increasing mean carrier diameter, but the opposite behaviour has been found. This can only be explained by an even greater increase in the adhesive force with increasing carrier diameter. So, when agglomerates are involved, they seem to be attached with a relatively high adhesive force, which is plausible in the way that the inertial forces that increase the cohesive forces between the drug particles on the carrier surface (which results in

size enlargement and thus, in a higher F_R), also increase the adhesive forces between drug and carrier particles during mixing (increasing F_A). It may also be that the easily detached fraction consists of the largest primary drug particles attached to carrier sites that are in good reach of frictional removal forces. Fig. 6.3C shows that the largest drug particles have a relatively large diameter compared to the carrier particles of fraction 45-63 μm. They stick out from the carrier surface in a much more pronounced way than drug particles of the same size attached to carrier particles of fraction 150-200 μm (Fig. 6.3D), and are relatively large compared to the size of carrier surface irregularities as well. Therefore, the mechanism of detachment may be different for different carrier fractions and it needs further investigation to come to conclusive explanations.

3.5. Changes in detachment rate within the first half second of inhalation

Because the highest drug release rate is within the first half second of inhalation (Figs. 6.1 and 6.2), more detailed information within this first phase of inhalation is desired. This has been obtained from laser diffraction experiments, since establishing a stationary powder circulation inside the classifier for inhalation times shorter than 0.5 s is not possible. It takes some time to achieve the preset flow rate and to accelerate the particles inside the classifier to a stationary velocity, whereas particle circulation is neither stopped immediately when the flow is switched off. During the laser diffraction experiments, the optical concentration (C_{opt}) in the aerosol from the inhaler was measured continuously. C_{opt} represents the particle concentration in the aerosol.

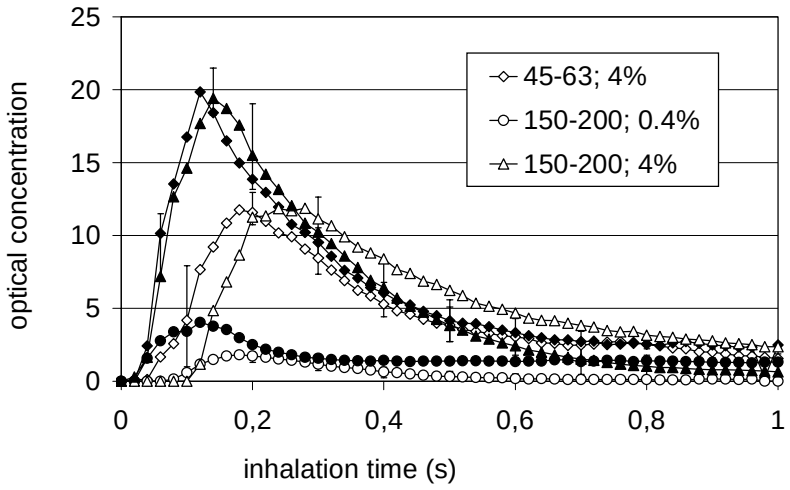

Figure 6.8. Optical concentration of the aerosol cloud as function of the inhalation time for three different formulations at two different flow rates: open symbols refer to inhalation at 30 l/min; closed to 60 l/min. All curves are the mean of three inhalations. The spread bars indicate the maximum and minimum values obtained. To make the bars recognisable, they have not been given for all data points and all curves.

Because the results showed that changes in the size distribution of released drug particles within the first second of inhalation were relatively small, C_{opt} is an acceptable measure for the amount of detached particles (from carrier) per unit time. C_{opt} as function of the inhalation time is shown in Fig. 6.8 for the first second of inhalation. The results from the mixtures with the finest carrier fraction (45-63 μm) and 0.4% drug (at 30 and 60 l/min) have

been excluded from presentation, because of some minor carrier passage, making the C_{opt}-signal less accurate. In addition to differences in peak value, which can be explained by different release rates (mg drug per second), yielding different particle concentrations in the aerosol, there are differences in the time necessary to reach the peak value. These differences partly reflect the time necessary to establish the preset flow rate and to accelerate the particles inside the classifier to a stationary velocity. On average (for all mixtures) it takes about 0.18 to 0.24 s at 30 l/min versus 0.12 to 0.14 s at 60 l/min to reach peak-C_{opt} (Fig. 6.8). These acceleration effects cause a minor deviation from a first order process in the first half second of inhalation.

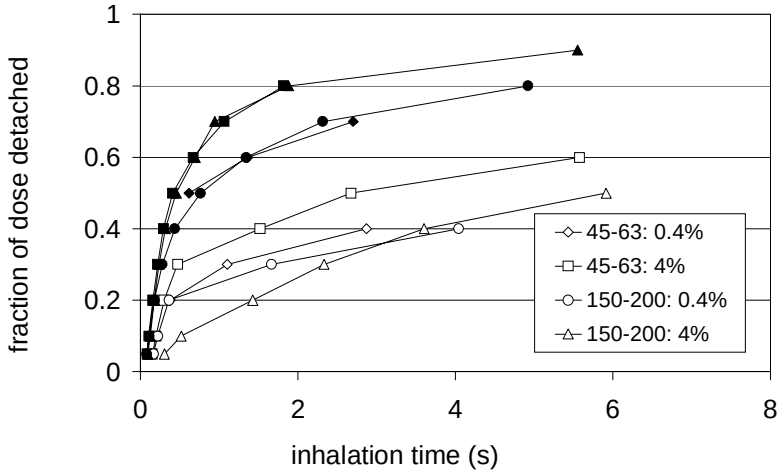

Figure 6.9. Fraction of the dose detached as function of the inhalation time for the mixtures presented in Figs. 6.1 and 6.2. In this figure, the data from laser diffraction analysis of the aerosol cloud (C_{opt}-measurement for $t < 0.5$ s; $n = 3$ per data point) and carrier residue measurement (for $t > 0.5$ s; $n = 2 \times 5$ per data point) have been joined together according to procedures described in the section materials and methods. Open symbols refer to data obtained at 30 l/min; closed to data obtained at 60 l/min. The order of magnitude for the spread can be derived from Fig. 6.8 for the laser diffraction data and Figs. 6.1 and 6.2 for the carrier residue data.

Comparison of the calculated drug detachment rates from laser diffraction analysis (0 to 0.5 s) and carrier residue measurement (> 0.5 s) respectively, is made in Fig. 6.9. The figure confirms that the differences in detached fraction of the dose arise particularly in the first second of inhalation. Fig. 6.9 also shows that the rate of drug particle detachment at 60 l/min is practically the same for both carrier size fractions in this study. However, at 30 l/min when the ratio of the (mean) separation forces to the (mean) adhesive forces is less extreme, and increasing the adhesive forces by press-on forces during the mixing process become more relevant, differences in drug release rate occur between the size fractions.

3.6. Implications for drug formulation and inhaler design

The results of this study confirm the relevance of frictional and inertial press-on forces during mixing to the inter-particulate forces in the powder mixture. When larger carrier particles are used, the degree of agglomeration of drug particles on the carrier surface increases (Table 6.1). But the obtained increase in removal forces during inhalation from this size enlargement is overcompensated by a much stronger increase in the adhesive forces between the drug and carrier. Also increasing the mixing time appears to increase the adhesive forces, particularly at lower payload. This may be attributed to drug particle re-

location from carrier sites with lower bonding capacity to more active sites. The results also show how important it is to balance between the adhesive forces in the mixture and the removal forces during inhalation. When the removal forces are high enough (e.g. at 60 l/min in the classifier based test inhaler used for the study), there is no effect of the carrier size fraction on the detachment rate, nor on the fraction of drug detached (Fig. 6.9). At high F_R, there is only an effect of carrier payload, the highest fraction of drug being detached for the highest payload, which shows that an excess of drug particles relative to the number of active sites is desired. Finally, it has been shown that drug detachment from carrier particles continues over a relatively long period (at least several seconds) at stationary flow conditions. As a result of the high initial detachment rate within the first half second of inhalation, sustaining the action of the removal forces (doubling the time) has approximately the same effect as increasing the size of these forces (e.g. by doubling the flow rate). This finding may have great practical implications. At least, it seems to indicate that the potential of inhaler design for improvement of the fpf from a dose is much greater than the potential of optimising the powder formulation. Particularly a controlled residence time for the powder dose in an effective de-agglomeration principle is recommended in this respect. This has the advantage that the same fpf can be achieved at a much lower inspiratory flow rate, which is beneficial to drug deposition in the respiratory tract. Considering the recommendations that the total dose is inhaled in 2 l, a residence time between 0.5 and 1.5 s seems preferable.

4. Conclusions

It has been shown that the initial rate at which drug particles are detached from carrier crystals in a classifier during inhalation, depends on the flow rate, the carrier payload and the carrier size fraction. The effect of carrier size fraction on the detachment rate in the first second of inhalation at lower flow rates is particularly relevant at higher carrier payloads. Drug release rate constants have been calculated, assuming a first order detachment process. This assumption appears to have meaning for the first half second of inhalation, but it has been shown that the release rate constant decreases dramatically with increasing inhalation time. This suggests that the drug concentration on the carrier surface is not the only variable. The ratio of removal to adhesive forces decreases as the carrier residue decreases, which can have different reasons: either the removal force decreases or the adhesive force increases after significant fractions of drug have been dislodged from the carrier (or both). There is strong evidence for an increase in the adhesive force due to the action of press-on forces during the mixing process, but another effect caused by drug agglomeration on the carrier surface during mixing (increasing F_R) can not be excluded. The experiments indicate that the fraction of drug that is dislodged during inhalation can be strongly increased by sustaining the action of the separation forces for a period of at least 0.5 to 1 s, and at lower inhalation flow rates even for a period of 1 to 2 s. This requires development of a classifier with adequate control of the residence time of the powder.

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