Adhesive mixtures for powder inhalation
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CHAPTER 5

THE EFFECT OF CARRIER RUGOSITY ON DRUG PARTICLE DETACHMENT DURING INHALATION, IN RELATION TO CARRIER SIZE AND MIXING INTENSITY AT LOW CARRIER PAYLOADS

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5.1. Abstract

Drug (budesonide) detachment during inhalation from crystalline and carrier lactose carriers with different rugosities and size fractions was investigated over a range of low carrier payloads. It was found that the amount of residual drug on the carrier after inhalation (carrier residue: CR) differs between coarse and fine crystalline carrier fractions. The difference increases with decreasing carrier surface payload (mg/m$^2$). This is explained by the existence of pseudo active sites (smooth crystal planes where adhering drug particles are exposed to press-on forces during mixing). Such press-on forces increase the interparticulate forces between the drug and carrier particles in mixtures with coarse carrier fractions. Measurements with an ISF inhaler showed similar trends in CR as found for the test inhaler, only the detachment was lower because the ISF inhaler generates has a less effective de-agglomeration principle. Granular carriers can provide shelter from press-on forces, because drug particles can be stowed in their surface cavities. It has been found that the degree of sheltering depends on the type and volume of the carrier surface cavities, as well as on the mixing conditions. The smaller the cavities and the milder the mixing process are, the higher the fraction of drug becomes that is detached during inhalation. However, the relevance of these parameters depends strongly on the carrier payload. Therefore, careful balancing between carrier payload, carrier surface topography and mixing conditions will be necessary to obtain maximal drug redispersion during inhalation.
5.2. **Introduction**

Recently, some new highly potent anti-asthma drugs have been marketed. The reduction in dose to amounts smaller than 20 µg is further stretching the performance requirements for the dry powder formulations used for these drugs. For instance, formoterol fumarate (Novartis Foradil®) in a metered mass of 25 mg requires a carrier payload of only 0.05% to obtain a dose of 12 µg (Schlimmer, 2002; Dubois et al., 2003). Also tiotropium bromide (Boehringer Spiriva HandiHaler®) is a highly potent active substance given in a dose of 18 µg as a dry powder (Dahl et al., 2003). Also with these low carrier payloads a sufficiently high and reproducible fine particle fraction must be obtained. In a previous study, it was shown that drug particle detachment from (lactose) carrier crystals during inhalation tends to deteriorate when the drug concentration in the adhesive mixtures is decreased. This was observed was for all (crystalline) carrier size fractions at a high flow rate, and particularly for fine carriers at a moderate flow rate (Dickhoff et al., 2003). The deterioration started already at payloads > 0.4% (w/w). One way to cope with this problem is to reduce the metered mass. For instance, the metered mass of tiotropium bromide is approx. 3.5 mg. As a result, the drug concentration in the formulation is kept at 0.5% (w/w), which is still acceptable from the viewpoint of drug redispersion during inhalation. However, low metered masses are not always possible. There is a limit to the amount of powder mixture that can be metered by, or discharged from the inhaler dose mechanism during inhalation accurately, and the limit may be different for different inhaler designs. Dry powder inhalation also finds increasing interest for the pulmonary delivery of systemically active agents (Ganderton, 1992) like peptides and proteins (Niven et al., 1994; Patton et al., 1999). In contrast with the previously mentioned new anti-asthma drugs, such active substances are given in a high dose, particularly when they have to be stabilized with sugar glass technology before they can be administered as a dry powder (Skyler et al., 2001; Maa et al., 2004). In sugar glass formulations, the excipient in the solid dispersion with the drug determines largely the dose weight given. Also antibiotics like colistin sulfomethate and tobramycin in cystic fibrosis therapy are administered in high dose ranges (160 to 300 mg). With these developments, the total range of carrier payloads in adhesive mixtures for inhalation has to be extended dramatically.

Developments in dry powder inhalation technology also include the introduction of new inhaler types. These new inhalers may have different mechanisms for the separation of drug and carrier particles during inhalation. For instance, the Airmax™ (IVAX), TwistiHaler™ (Schering-Plough) and Novolizer™ (Viatris) generate inertial separation forces instead of turbulent shear or frictional forces. Inertial forces enable successful detachment of drug particles not only from smooth carrier surfaces, but also from carrier irregularities. Therefore, these new inhalers have generally higher de-agglomeration efficiencies than most currently available devices and a high carrier rugosity may not be a problem (de Boer et al.,
2003; Dickhoff et al., 2005). Consequently, much coarser carrier fractions can be used as the carrier applied in turbulent shear inhalers, which improves the dose accuracy. In fact, very fine carrier fractions do not always perform best in these new inhalers because a certain residence time in the classifier of the Novolizer™ or in the cyclone of the Airmax™ is required to make maximal use of the available energy within the inhaled air stream. Generally, the residence time in the cyclone type of circulation chambers decreases with decreasing mean carrier diameter as a result of a decreasing ratio of centrifugal force to drag force (de Boer et al., 2003). Coarse carrier particles normally have a higher surface rugosity than fine carrier particles, because the size of surface discontinuities of (industrially produced) carrier crystals increases with the diameter of the crystal. A high carrier rugosity may reduce the efficacy of inertial and frictional press-on forces during mixing which increase the interparticulate (drug-to-carrier) forces in the mixture (Dickhoff et al., 2005). Drug agglomerates tend to accumulate in the carrier surface cavities during mixing where they find shelter from these press-on forces. Besides, drug agglomerates in cavities are exposed to much higher inertial separation forces during inhalation than single drug particles (Louey et al., 2003). Obviously, this may contribute to a greater drug particle detachment. Therefore, carriers with a high surface rugosity may be advantageous for the new generation of inertial separation inhalers, but the optimal conditions for this sheltering have not yet been found. These conditions are related to parameters such as size and shape of the carrier irregularities and the mixing conditions. If the carrier cavities are too large, or if the mixing is too violent (or too long), agglomerates inside these cavities may also be detached during the mixing process and be redistributed over the carrier surface, where they become in reach of the press-on forces. Finally, the sheltering capacity (storage volume) has to be balanced in relation to the desired carrier payload (Dickhoff et al., 2005).

Summarizing, it can be concluded that new drug and inhaler developments require extension of the investigations on the effects of carrier payload and carrier rugosity. In previous studies, we have focussed particularly on the higher drug concentrations, up to and including 8% (w/w) (Dickhoff et al., 2003; 2005). The aim of this study is to investigate the drug detachment during inhalation with a classifier based test inhaler for mixtures with payloads in the range between 0.05 and 4% (w/w) for crystalline and granular carriers. Granular carriers with differently sized surface discontinuities were used for this study. Additionally, the mixing conditions (with a Turbula mixer) for these granular carrier fractions were varied from mild (20 rpm) to relatively violent (90 rpm) in order to establish the optimum conditions. To investigate the general applicability of our observations and conclusions experiments were also carried out with a different inhaler, having a different de-agglomeration principle.
5.3. Materials and methods

5.3.1. Starting materials

Three different carrier fractions (63-90, 150-200 and 250-355 µm) of crystalline alpha lactose monohydrate were derived from Pharmatose 80M (DMV International, Veghel, The Netherlands). The fractions were obtained by 30 min vibratory sieving (Fritsch Analysette 3, Germany) followed by 20 min of air jet sieving (Alpine A200, Augsburg, Germany). Pharmatose 100M, 200M, 325M and 450M were used to make granules with different surface textures. Micronized budesonide was supplied by Sicor (Milan, Italy). The volume median diameter (VMD = \(X_{50}\)) of the budesonide used was 1.42 µm (\(X_{10}\): 0.60 µm, \(X_{90}\): 2.96 µm).

5.3.2. Lactose granulation and preparation of carrier size fractions

Granular carrier materials with different rugosities were prepared by agglomeration of different crystalline lactose starting materials (100M, 200M, 325M and 450M). Granulation was performed in a batch size of 1 kg, using a high shear mixer granulator Gral 10 (Machines Collette, Wommelgem, Belgium) and 160 ml of water as binder liquid added at a rate of 20 ml/min. Impeller and chopper speed were adjusted to 600 rpm and 3000 rpm respectively, and after wetting, a kneading phase of 3 min was applied in order to obtain dense and strong agglomerates. After kneading, the wet mass was passed through an oscillating sieve with an aperture of 2 mm (Erweka, AR 4000, Heusenstamm, Germany) and dried in an oven at 40°C for 16 hrs. 250-355 µm sieve fractions were prepared as described for the crystalline carriers.

5.3.3. Characterisation of the starting materials

Particle size distributions of the starting materials were measured with a Sympatec HELOS compact KA laser diffraction apparatus (Sympatec GmbH, Clausthal-Zellerfeld, Germany), using a RODOS dry powder disperser (at 3.0 bar). Lenses of 100 mm (for the budesonide sample) and 200 mm (for the lactose fractions) were used and calculations were based on the Fraunhofer theory. All data given are the mean of at least three measurements.

The surface texture of the carrier fractions has been expressed as a ‘surface roughness index’ (SRI), which is the ratio of the specific surface area from nitrogen adsorption to the calculated surface area. Nitrogen adsorption (BET theory Branauer et al., 1938) was performed with a Tristar surface analyser (Micromeritics Instrument Corporation, Norcross, USA). Samples of approx. 1 g were inserted in test tubes and flushed with helium gas at 20°C for 2 h, prior to measurement. The calculated surface areas have been based on the arithmetic mean of the sieve fractions, assuming that particles are spherical.

The amount of impurities on the surface of the lactose crystals was measured with UV adsorption, using a UNICAM UV 500 (ThermoSpectronic,
Cambridge, UK) at 280 nm of a 5% aqueous lactose solution. Because solutions were clear, filtration was not necessary.

The Hausner ratio (Hausner, 1967) was computed as the ratio of the bulk density after tapping to that before 200 taps using an Engelsman Jolting volumeter (Ludwigshafen, Germany).

5.3.4. Mixture preparation and homogeneity testing

Mixtures were prepared in a stainless steel container of $160 \times 10^{-6}$ m$^3$, using a Turbula mixer (W.A. Bachofen, T2C, Basel, Switzerland) at 20 or 90 rpm for 10 min (batch size: 25 g). Mixtures with crystalline carrier fractions contained 0.05; 0.1; 0.2; 0.4; 1.0; 1.5 and 2.0% (w/w) budesonide, and mixtures with granular carriers contained 0.1; 0.2; 0.4; 1.0; 2.0 and 4.0% (w/w) of the same drug.

For calculation of the percent coverage of the carrier surface with drug particles, it was assumed that all (drug and carrier) particles are spherical and monodisperse with a diameter that equals volume median diameter ($X_{50}$-value) from laser diffraction analysis for the drug particles, and the arithmetic mean of the sieve fraction for the carrier particles. It was also assumed that the projection of each drug particle on the carrier surface is a square with a side that has the same length as the diameter of the particle (leaving 21.5% of the carrier surface uncovered).

Homogeneity was determined on 20 samples of 25 (± 1.0) mg per mixture. The samples were dissolved in 20 ml ethanol p.a. and the UV adsorption was measured at 243.7 nm, using a UNICAM UV 500 (ThermoSpectronic, Cambridge, UK).

5.3.5. Inhalers and carrier residue

The test inhaler (University of Groningen, The Netherlands) used for the inhalation experiments has been described previously (Dickhoff et al., 2003). This test inhaler has an air classifier type of de-agglomeration principle (inertia), which separates particles upon size. Theoretical cut-off values for crystalline (1 aq) lactose are 27 and 19 µm at 30 and 60 l/min respectively. The test inhaler has no dose system: individual doses of 25 mg were weighed and inserted manually. Large particles (or unbroken pellets) are retained and stay in circulation as long as there is an air stream through the classifier. After inhalation, the retained carrier particles were removed from the device and analysed for residual drug (carrier residue).

An ISF inhaler has been used as marketed reference inhaler (Salvatore, 1976). Powder de-agglomeration in this inhaler is primarily by turbulent shear (drag and lift forces). Furthermore carrier particle impaction against the inner wall of the capsule circulation chamber after discharge from the capsule may contribute somewhat to de-agglomeration. For the ISF inhaler individual doses of 25 mg were
weighed and filled in sealed inhalation capsules nr. 3. The first stage deposition during cascade impactor analysis was considered to represent the carrier residue.

5.3.6. Laser diffraction analysis of the aerosol cloud

Size analysis of the particles in the aerosol cloud from the test inhaler was performed with the same laser diffraction apparatus as described for characterization of the starting materials. The test inhaler was connected to a previously described inhaler adapter with flow control unit (de Boer et al., 2002). A lens of 100 mm was used and the start of each measurement was triggered on an optical signal of 0.05% on channel 30 and stopped after 3 s real measuring time. The flow rate through the test inhaler was adjusted to 10, 20 and 30 l/min, respectively. Each value presented, is the mean of ten doses and for each individual measurement a reference measurement was performed on the carrier without drug, in order to make corrections for released lactose fines.

5.3.7. Cascade impactor analyses (CIA)

In vitro deposition was tested with a Multi-Stage Liquid Impinger (MSLI) of the Astra type (Erweka, Heusenstamm, Germany), using the induction port described by the European Pharmacopoeia 4th Ed. 2002, with a special coupling flange for the test inhaler. Each impactor stage was filled with 20 ml ethanol p.a., except for the final stage, in which a 76 mm dry glass filter (Pall Corporation, type A/E, Michigan, USA) was inserted. The flow rate through the inhalers was adjusted to 30 or 60 l/min on the basis of the differential pressure across the inhaler measured at the position of the coupling flange. The inhalation time was 3 s.

After completion of a series of ten inhalations, the drug fractions on the impactor stages were allowed to dissolve for at least 1 h before they were collected. The drug solutions were processed in the same way as described for homogeneity testing. Fractions derived from the stages 3 and 4 and the filter are referred to as the fine particle fraction. All data given are the mean of two series of ten doses.

The in vitro aerosol deposition studies were conducted in an air conditioned room, where the ambient temperature and relative humidity (RH) were 19 ± 1°C and 50 ± 5% respectively.

5.4. Results and discussion

All mixtures prepared for this study showed a good homogeneity. The coefficient of variation for the drug content was below 3.3%, which is well within the recommended value of 4-5% (Dietrick, 1993). Table 1 summarizes some physical properties of the crystalline carriers used in this study.
Table 1: Some physical properties of the crystalline lactose carriers

<table>
<thead>
<tr>
<th></th>
<th>E280nm</th>
<th>BET</th>
<th>SRI</th>
<th>CSA</th>
<th>E280 / CSA</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>80M (63-90 µm)</td>
<td>0.055</td>
<td>0.1713</td>
<td>3.36</td>
<td>0.0509</td>
<td>1.08</td>
<td>1.20</td>
</tr>
<tr>
<td>80M (150-200 µm)</td>
<td>0.041</td>
<td>0.1607</td>
<td>7.22</td>
<td>0.0223</td>
<td>1.84</td>
<td>1.13</td>
</tr>
<tr>
<td>80M (250-355 µm)</td>
<td>0.032</td>
<td>0.1334</td>
<td>10.36</td>
<td>0.0129</td>
<td>2.48</td>
<td>1.10</td>
</tr>
</tbody>
</table>

*a,n=5 samples

5.4.1. The effect of carrier payload on particle detachment during inhalation

Fig. 1 presents the carrier residue (CR) as a function of the carrier payload at 30 and 60 l/min for mixtures with crystalline carrier fractions. Initially CR for all three carrier fractions decreases relatively quickly with increasing payload at both flow rates. Starting at a payload of approx. 0.4% (30 l/min) the decrease rates slow down and the curves start to diverge from each other. When the payload is further increased, CR for the coarse fraction rises again, whereas the decrease in CR for the fine fraction is further continued at a slower rate. The intermediate size fraction shows an intermediate behaviour. The differences in slope within the range of payloads between 0.4 and 2% may seem relatively small, but they are the introduction to considerable differences in CR at much higher payloads.

![Fig. 1: Carrier residue as function of the carrier payload (% budesonide) from different crystalline lactose carrier crystals (■ and □ 63-90, ○ and ● 150-200 and ▲ and ∆ 250-355 µm). Closed symbols refer to 30 l/min; open symbols to 60 l/min (n=2).]
The reason for this difference in behaviour between different carrier size fractions at higher payloads has been discussed previously (Dickhoff et al., 2003). A decreasing CR with increasing payload is the result of an increasing excess of drug particles relative to the number of strong bonding places (active sites). This reduces the mean adhesive force in the mixture between the drug and carrier particles. Basically, this is the same for all carrier size fractions. Yet, for a coarse crystalline carrier, CR starts to exhibit a different behaviour at payloads above 0.4% (w/w). This may be attributed to the action of inertial and frictional press-on forces during mixing. Such forces make the interactive forces in the mixture higher and are the result of carrier particle collisions in the mixing container. As explained before, the magnitude of these forces depends on the carrier diameter.

In Fig. 1, CR decreases with increasing payload in a comparable way for all three carrier size fractions at 30 l/min. The difference in specific surface area between the carrier fractions makes direct comparison of drug partition into fractions attached to weak and strong bonding sites difficult however. Therefore, Fig. 2 has been prepared which shows CR as function of the initial surface payload (in mg per square meter of carrier surface). In contrast with Fig. 1, the CR-curves for the coarsest and finest carrier differ increasingly from each other with decreasing payload (starting at a payload of approx. 300 mg/m²). This suggest that the distribution of drug over low and high binding sites is balanced differently between both carrier fractions at a low payload, which could be the result of a higher bonding capacity of the active sites for the coarse fraction. The CR-values at 60 l/min do seem to contradict this however. At this flow rate, when only particles attached to the strongest bonding (active) sites are not dislodged, CR is nearly the same for all fractions. When the removal forces during inhalation are sufficiently high, the increase in press-on forces is apparently no longer sufficient to influence the fraction of drug detached. This leads to the conclusion that the adhesive forces for drug particles (attached to the weak bonding sites) that have been increased by press-on forces are lower than the adhesive forces between drug particles that are attached to active carrier sites. The results in Fig. 2 at 60 l/min also suggest that the balancing of drug over strong and weak binding sites is approx. the same for all carrier size fractions and so are the number of active sites for these fractions. The absolute values for CR within the range of payloads between 0.4 and 2% in Fig. 1 are somewhat different from those reported in a previous study, which may be a consequence of different batches of lactose and budesonide used for both studies.
If the fraction of particles that remains attached at 60 l/min (CR) is approx. the same for all carrier size fractions (as shown in Fig. 2), and the size distributions for the drug particles that are not attached to the active carrier sites are the same too, a decrease in the flow rate should cause the same shift in CR towards higher values for all carrier fractions. This, because the ratio of removal ($F_R$) to adhesive forces ($F_A$) changes in a same way for all fractions. The finding that this does not occur (Fig. 2), means that the size distributions of the adhesive forces for particles attached to weak bonding places are different for the different fractions. This can be explained with the action of press-on forces at low payloads on so-called ‘pseudo active sites’. Pseudo active sites here are defined as smooth crystal planes that make contact with each other during the mixing process when carrier particles collide with, or roll over each other. They do not have a high binding potential of their own, at least not compared with the active sites in terms of places where increased contact areas or multiple contact points are possible. But particles attached to such planes are subjected to the inertial and frictional press-on forces during mixing, which increases the drug-to-carrier interaction forces compared to carrier sites where these press-on forces are not effective. It is known from the literature and previous studies that drug particles are wiped together in carrier surface discontinuities during the course of the mixing process (Kulvanich and
Stewart, 1987; Iida et al., 2003). However, initially, a random distribution of drug particles over all types of carrier sites is more likely. Obviously the attachment forces of particles initially deposited on smooth planes may increase most strongly in mixtures with coarse carrier particles. Therefore, pseudo active sites exist primarily for coarse carrier size fractions. They do increase the total number of strong binding places and by that, the number of drug particles that is necessary to get the same carrier residue as obtained for mixtures with fine carrier fractions at the same carrier surface payload. This explains why the CR-curves for the coarse and fine carrier fraction deviate from each other at low payloads when low de-agglomeration forces are applied.

5.4.2. The effect of carrier rugosity on drug particle detachment during inhalation

Particles may be sheltered from the press-on forces during mixing in carrier surface discontinuities (Dickhoff et al., 2003; 2005). The sheltering capacity and efficacy depend on the type and volume of the discontinuities and the mixing process respectively. It has been shown that granular carriers, with a high surface rugosity, exhibit an increased storage capacity (Dickhoff et al., 2005). A high rugosity does not necessarily guarantee a high sheltering efficacy however. During mixing, large drug agglomerates may be removed from the carrier surface cavities again by action of the same type of forces that also occur during inhalation. Additionally, extremities of granular structures may be able to project into the cavities of neighbouring carrier particles in the mixture. Therefore, not only the total volume of the carrier discontinuities is important; also the size and shape of the individual pores could be relevant. Moreover, our hypothesis implies that there should also be an effect of the mixing conditions. Fig. 3 shows the carrier residues as a function of the payload for four different granular structures, having the same size fraction of 250-355 µm. A similar initial decrease in CR as for crystalline carriers has been obtained, but the minimum occurs at a much higher payload (between 1 and 2% w/w). Also the minimum CR-values of most granules are slightly lower than that for the crystalline size fraction of 250-355 µm (Fig. 1), which supports the theory of the existence of pseudo active sites. Specifically, in granular structures there are less smooth crystal planes that are accessible to press-on forces. This is best shown in Fig. 4 which compares a crystalline carrier with two granular carriers composed of primary particles with different median diameters. The crystalline carrier has the lowest storage volume (sheltering capacity) for the drug (shaded areas) and the largest smooth crystal planes on its outer circumference. These large crystal planes are the pseudo active sites. The coarse granular structure has an increased sheltering capacity and reduced area for pseudo active sites. The fine granular structure has approx. the same storage volume as the coarse granule, but the drug agglomerates inside the individual pores
are much smaller (increased sheltering efficacy), whereas there are only few pseudo active sites available.

Fig. 3: Carrier residue as function of the carrier payload (% budesonide) from different granular carriers made from: ■ 100M, ♦ 200M ▲ 325M and × 450M, at 30 l/min.

Fig. 4: (A) a coarse crystalline carrier (B) a granule which has large cavities and (C) a granule which has small but many cavities.

The results in Fig. 3 are in agreement with predictions. The highest carrier residue has been obtained for the granules with the largest primary particles (Pharmatose 100M), and therefore largest pores. The large drug agglomerates in
these pores, with high masses, are subjected to the highest inertial forces, not only during inhalation Louey and Stewart, 2002, but also during mixing of all agglomerate carriers. This results in the highest degree of drug redistributed over circumferential crystal planes during mixing, and thus the highest effect of the press-on forces during mixing. The minimum in CR for the 100M granulate is also obtained at a relatively low carrier payload compared with the other mixtures in Fig. 3. Because there exists no method to characterize the drug storage capacity and efficacy adequately, the ratio of median drug diameter to median primary particle diameter in the granule (both obtained from laser diffraction analysis) has been used to distinguish between the different granular carriers. Fig. 5 shows the minimum value for CR (trough value), as well as the payload at which this trough is found as function of this ratio. To obtain the precise minimum values for CR, fitting has been applied on the curves in Fig. 3 (using hyperbolic functions). It can clearly be seen that the interesting range of diameter ratios is between 0 and 20 (to 40) under the mixing conditions used. In this respect, the 100M granule is not an optimal agglomerate.

Fig. 5: Carrier residue (CR) when the trough is reached (■) and payload at which the trough occurs (▲) as function of the diameter ratio between the size of the primary particles of the granule ($X_{50}$ from laser diffraction) and the size of the primary particles of budesonide ($X_{50}$ from laser diffraction).

5.4.3. The effect of mixing conditions on drug detachment during inhalation

If large drug agglomerates can be removed from the carrier surface cavities during mixing, mixing intensity must have an effect. In a similar way as during inhalation, it may be expected that the extent of drug relocation depends on the magnitude of the inertial forces that are responsible for this removal. Fig. 6 proves
that this is indeed true for two different payloads of 0.4 (A) and 4.0% (B) w/w. In these figures the results from cascade impactor analysis (30 l/min) are presented for mixtures prepared using two different mixing intensities (20 and 90 rpm) in the Turbula mixer. In addition to the carrier residue, the stage 3, 4 and filter depositions are shown. It should be mentioned that the test inhaler used for the experiments was not designed for drug delivery to the respiratory tract, but for carrier residue experiments only. As a consequence, mouthpiece accumulations are quite high.

Fig. 6A indicates that coarse granular carriers have hardly any advantage over crystalline carriers at a relatively low payload of 0.4% when violent mixing conditions are applied. In the same size fractions of 250-355 µm, granules composed of smaller primary particles do have a much larger surface area to which drug particles can adhere. Consequently, the excess of drug particles relative to the number of active bonding sites is much lower. The precise effect of this aspect is difficult to assess however, as it is opposite to that of a reduced number of pseudo active sites. When larger drug agglomerates are being removed from the carrier cavities during mixing (at 90 rpm) and divided into smaller portions (or even primary particles), the redistribution of drug particles over the entire carrier surface may be relatively high. If however the mixing intensity is reduced (to 20 rpm), the removal forces are decreased, larger drug agglomerates remain within the cavities of the granular structure. This leads to reduced occupation of (pseudo) active sites and higher removal forces during inhalation. This explains why the CR, for mixtures prepared at 20 rpm, is approx. 50% of the value obtained at 90 rpm (for the granular carrier only).
At 4.0% (Fig. 6B) payload there is an advantage of granular structures for both mixing intensities (at least for air classifier type of inhalers). In contrast to the lower payload, there is also an advantage of lower mixing intensity for the crystalline carrier. The reasons have already been explained. For a crystalline carrier, reduction of the mixing intensity is a reduction of the press-on forces that increase the interaction forces in the mixture. For the granular carriers, there is a reduced disintegration of large drug agglomerates into smaller agglomerates that have a lower inertia and are subjected to lower inertial removal forces during inhalation. Fig. 6 confirms that maximal drug detachment (during inhalation) from granular carriers must be obtained from selecting the optimal combination of carrier payload, type and volume of the carrier surface pores and mixing conditions. Under these conditions, a CR of only 20% is possible at a relatively low inspiratory flow of 30 l/min, as shown for the 450M granulate prepared at 20 rpm in a Turbula mixer with a payload between 0.4 and 4.0% w/w. Although Fig. 6 shows that an increase in the mixing intensity from 20 to 90 rpm increases the carrier residue of granular carriers dramatically, there appears to be no influence of carrier pore size on this increase, which is somewhat surprising. For both granular carriers (100 and 450M), as well as, at both payloads, the increase in carrier residue is approx. a factor of 2.

5.4.4. The effect of inhaler design on drug detachment during inhalation

Results in this study so far have been obtained using inertial separation forces for the drug particles during inhalation. To investigate whether similar
trends can be found when other types of separation forces (in different inhaler designs) are applied, an ISF inhaler has been used for detachment experiments with the two extreme crystalline carrier fractions in Fig. 1 (63-90 and 250-355 µm respectively) at 30 and 60 l/min. For this inhaler, drug particle detachment from carrier crystals is mainly the result of turbulent shear (drag and lift forces), although a minor contribution from inertial forces may not be excluded. Carrier particles impact mildly with each other and with the inner walls of the capsule while the capsule rotates during inhalation. Particles may also collide somewhat more violently with the inner wall of the circulation chamber upon discharge from the capsule, but this is only a single collision. Because the ISF inhaler does not retain the carrier particles, the first stage deposition in the MSLI has been measured to assess the fraction of drug not detached during inhalation. Considering that the cut-off value for the first stage of this impactor is 23.8 µm at 30 l/min, it may be expected that all carrier particles are collected on the first stage.

Fig. 7 shows these first stage depositions (CR values) for the same mixtures as used for Fig. 1. All CR-values are much higher than in Fig. 1, particularly at 60 l/min, but the observed trends are largely the same. Initially, CR decreases with increasing drug concentration in the mixture, whereas at higher payloads CR of the mixture with the coarsest carrier starts to increase again. The higher CR-values at all payloads and for both flow rates (compared to Fig. 1) confirm that inertial forces are more effective in detachment of drug particles from carrier crystals during inhalation than drag and lift forces. However, the reduction of removal forces for all mixtures, does not change the relative differences in performance between the mixtures that are controlled by the size distributions of the adhesive forces. Therefore, the trends in Figs. 1 and 7 are the same.
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5.5. Conclusions

The present study shows that application of very low payloads, in adhesive mixtures, for dry powder inhalation is unfavourable. It has been explained that this is due to an excess of active sites relative to the amount of drug particles present in the formulation. In the range of payloads < 0.4% w/w, the carrier surface properties seem to be of greater significance than the bulk properties to drug particle detachment. The adhesive forces between drug and carrier particles, which are increased by press-on forces during mixing, are of smaller than those between drug particles and the active sites of the carrier particles. At least, the influence of the press-on forces is not noticeable after increase of the inhalation flow rate from 30 to 60 l/min.

Coarser crystalline carriers generate larger press-on forces during mixing than the finer carriers. This results in the existence of pseudo active sites on their smooth surfaces, which explains why at lower payloads increasing differences occur in the detachment from coarser and finer carriers. For agglomerated carriers, the occurrence of larger crystal planes on the circumference of the agglomerate where press-on forces may be effective is reduced compared to crystalline carriers.

In this study, it has been shown that coarse granular carriers have an advantage over crystalline carriers (with the same size) at a relatively high payload of 4% when inertial separation forces are applied during inhalation. Drug particles
in the surface cavities of granular carriers find better shelter from the action of the press-on forces during mixing. At lower payloads, the advantage is confined to mild mixing conditions. Under violent mixing conditions, drug particles are distributed more effectively over the entire surface area of the granular structures, which is larger than that of crystalline carriers at the same size. Consequently, the excess of active sites relative to the number of drug particles is larger than that for crystalline carriers. All results considered, it may be concluded that it depends on the balancing between the carrier payload, the type and shape of the carrier surface irregularities and the mixing conditions whether granular carriers are an advantage or not (for inhalers generating inertial separation forces). The optimal combination of conditions is difficult to predict however, because of the opposite effects from increasing the specific surface area (binding capacity of the active sites) and increasing the sheltering capacity. Finally, it can be concluded from the experiments with the ISF inhaler, that the factors that increase the interparticulate forces in the mixture (active sites and press-on forces) are also relevant to inhalers that rely primarily on turbulent shear for drug redispersion during inhalation.

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5.6. References


