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Research paper

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

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Abstract

The effect of carrier payload and mixing time on the redispersion of drug particles from adhesive mixtures during inhalation for two different drugs (budesonide and disodium cromoglycate) has been investigated. A special test inhaler which retains carrier crystals during inhalation was used at 30 and 60 l/min. The special inhaler enabled the analysis of residual drug on the carrier yielding so called carrier residue (CR) values. Mixtures with carrier size fractions of 32–45; 150–200 and 250–355 μm, derived from marketed lactose brands, with increasing carrier payload (0.4–6.0% w/w of drug) were prepared. It was found that with increasing carrier payload, the CR increases for the coarse carrier fraction, decreases for the fine fraction and remains roughly constant for the intermediate fraction at 30 l/min. At 60 l/min, the CR decreased for all carrier fractions with increasing payload. The effect of powder bulk properties on the adhesive forces between drug and carrier (during mixing) as well as changes in the balance between adhesion and separation forces (during inhalation) explain the results found. An improved understanding of the different effects is obtained through the recently introduced force distribution concept. The ratio of (mean) separation force to (mean) adhesion force increases with the flow rate. The adhesive forces (during mixing) increase with increasing carrier diameter (higher press-on and kneading forces) and longer mixing time.

Keywords: Adhesive mixtures; Bulk properties; Budesonide; Disodium chromoglycate; Mixing time; Lactose; Carrier payload

1. Introduction

Interest in the delivery of therapeutic drugs via the respiratory tract using dry powder inhalers is rapidly expanding. For an effective inhalation therapy, micronized drug particles in an aerodynamic size range of 1–5 μm [1–4] are needed to obtain deposition in the lower respiratory tract). Such micronized drug particles are very cohesive and their flow properties are poor [4]. Therefore, without further processing (e.g. preparation of adhesive mixtures or spherical pellets [5]) dose reproducibility would be insufficient. Relatively large carrier particles, usually alpha lactose monohydrate crystals [6], are often incorporated in the formulation. Such carrier particles generally exhibit good flow properties, which improve the dose measuring reproducibility of the mixture with the micronized drug. It has been recognized for adhesive mixtures, that the type and size of the interaction forces between the carrier and the drug particles determine the de-agglomeration of the powder during inhalation [7].

The dominant interaction forces between the drug and carrier particles in adhesive mixtures are Van der Waals forces [8,9]. The size of the forces has to be optimized with respect to good mixture stability and obtained fine particle fraction during inhalation. In fact, this is an optimization between the adhesive forces in the mixture and the detachment forces generated during inhalation, as has been discussed previously with the introduction of a novel force distribution concept (FDC) [10]. Many factors that influence the drug-to-carrier interaction are known. They include the cohesiveness of the drug, carrier surface

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properties, mixing conditions (e.g. type of mixer), carrier bulk properties and carrier payload. In particular, the effect of carrier surface properties has been studied quite extensively.

Stephenson and Thiel [11] presented the production of an interactive mix (adhesive mixture) as a two-step process. In order to adhere single cohesive particles onto the carrier crystals, the mixing process must first break down aggregates of the fine powder. Staniforth [12] describing the 'total mixing concept', was the first to show that mixing of fine and coarse particles together leads to a dynamic equilibrium between an adhesive and non-adhesive mix. Aulton and Clarke's [13] formulation that there exists a competition between cohesion and adhesion, is in agreement with Staniforth's 'total mixing concept'. Staniforth's [14], 'order out of chaos' theory extended this with the notion that the outcome of this competition (between cohesion and adhesion) is uncertain. He explained that the equilibrium can be changed in the direction of adhesion, by size reduction of both components or by enlargement of the surface of the coarse component, for instance by applying a high surface rugosity, in which interlocking through multiple interparticle contacts can occur. This prevents removal of the adhered particles due to abrasion, as the adhered particles experience a certain protection against various removal forces.

In another study, Staniforth et al. [15] showed that large particles of recrystallized lactose with a more porous structure exert stronger adhesion forces on drug particles than smaller crystal carriers and therefore, result in more stable mixtures. Others [16,17] found identical results with mixtures containing carriers with high rugosity. Such mixtures appeared to segregate to a lesser extent than those containing smoother carriers.

In various studies, it has been shown that in vitro respirable fractions obtained from smaller lactose particles are higher than those obtained from coarse lactose particles [6,18,19]. This is explained by de Boer et al. [20] who showed that fine carrier fractions contain less impurities and have lower rugosities, as a result of which not only the interaction forces may be lower but also the removal forces are more effective. They suggested that drug particles (and adhering fines) on large carrier crystals may accumulate in the irregularities of the carrier surface or against steep slopes, where multiple contact points as well as increased adhesion forces are possible. On these sites, drug particles not only find shelter from friction and shear forces during mixing, but also from drag, shear and friction forces during inhalation.

Various attempts to improve the delivery efficiency of drug particles to the lungs have been made by controlling the particle shape and surface (roughness, smoothness and impurities). Increasing the smoothness of the carrier has shown to increase the fine particle detachment of drug particles [21–27]. Therefore, it has been recommended, to use carrier particles with a low surface rugosity for inhalation (powders) [28,29]. Special crystallization techniques, using Carbopol gel as crystallization medium [30], and granulation processes [31,32] have been used to control the carrier surface rugosity either to a minimum or to the extreme. Recently, in vitro studies with adhesive mixtures with a ternary component, such as fine lactose particles [22,24], or so-called force control agents like magnesium stearate [6,33], isoleucine [19], etc., have been shown to enhance the detachment of drug particles from the carrier lactose particles during inhalation. Another method introduced recently is manipulation of the drug particle size distribution [34].

In previous studies, the effect of carrier particle size [23,27,35–39], carrier payload [2,19] and mixing time [36,40] on the fine particle fraction during inhalation has been investigated. In contrast, the influence of the carrier bulk properties during mixing on the drug-to-carrier interaction has hardly been described. This is quite surprising, because the possible relevance of bulk properties was already been recognized years ago. Timsina et al. [2] suggested that the drug-to-carrier ratio may affect the carrier bulk properties and they investigated the effect of press-on forces on the adhesive forces between drug and carrier particles too. Podczeck [41] showed that the adhesive forces between drug particles and a carrier substrate increase when particles are pressed onto each other with increasing forces. Adhesive forces will increase with increasing press-on forces during mixing too and, drug particles that are attached to large carrier crystal planes are subjected to these press-on forces more effectively than particles hidden in carrier surface discontinuities. High inertial press-on forces during mixing can be the result of the bulk properties of the powder, as has been shown recently for two different carrier sieve fractions [42]. With increasing mean carrier diameter, the flow properties improve whereas the Hausner ratio decreases. This causes the inertial and friction forces (the press-on forces) within the powder during mixing to increase. It has also been shown that carrier surface rugosity and impurity increase with increasing mean carrier diameter and thereby, the number of active sites in terms of multiple contact points, increased contact areas and capillary forces [10]. So, there are two reasons why fine particle redispersion during inhalation might deteriorate with increasing carrier particles size. It should consequently be realized that previously supposed carrier surface effects, could partly have been a bulk effect too in some studies (e.g. ref. [22]).

The aim of this study was to investigate the effect of carrier particle size (bulk property) on the fine particle detachment during inhalation, using two different drugs (budesonide and disodium cromoglycate), different carrier payloads and different mixing times. The study was carried out with four different α-lactose monohydrate sieve fractions derived from marketed brands. A special test inhaler [10,43] with carrier retainment was used in combination with a cascade impactor at two different flow rates (30 and 60 l/min). Conclusions based on the amounts

of drug still attached to the carrier crystals after inhalation were formulated in terms of the achieved balances between adhesion and cohesion forces in the mixture, the adhesive and removal forces during inhalation and carrier bulk and surface properties, respectively.

2. Materials and methods

2.1. Starting materials and test inhaler

Fractions of crystalline alpha lactose monohydrate as carrier material were derived from different Pharmatose types (DMV International, Veghel, The Netherlands) by 30 min vibratory sieving (Fritsch Analysette 3, Germany) followed by 20 min of air jet sieving (Alpine A200, Augsburg, Germany). Pharmatose 100 M was used as starting material for the fraction 32–45 μm, whereas Pharmatose 80 M yielded the fractions 45–63, 150–200 and 250–355 μm. Sofotec (Frankfurt, Germany) supplied two different budesonide samples (due to insufficient material), which is a hydrophilic drug, whereas disodium cromoglycate (dscg; a lipophilic drug) was supplied by Sicor (Italy).

A test inhaler, University of Groningen (Fig. 1), was used for the inhalation experiments [10,34]. This test inhaler has an air classifier for the separation of airborne particles upon size (inertia): with theoretical cut-off values for lactose of 27 and 19 μm at respectively 30 and 60 l/min, so only small particles are discharged. Larger particles (or unbroken pellets) are retained and stay in circulation as long as there is an air stream through the inhaler. After inhalation, the retained carrier particles were removed from the device and analyzed for residual drug (carrier residue).

2.2. Characterization 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 dispenser (at 3 bar). Lenses of 100 mm (for the budesonide and dscg samples) and 200 mm (for the lactose fractions) were used and calculations were based on the Fraunhofer theory. All data given are the mean of two measurements.

2.3. Mixture preparation and homogeneity testing

The formulations for the carrier payload experiments were prepared by mixing 25 g lactose (from each of the different fractions 32–45, 150–200 and 250–355 μm) with 0.4, 1.6, 3.0 and 6.0% (w/w) budesonide, respectively dscg, in a stainless steel container of 160 cm^3, using a Turbula tumbling mixer type T2C (W.A. Bachofen, Basel, Switzerland) at 90 rpm for 10 min. Formulations for the mixing time experiments were prepared by mixing 0.4 and 4.0% w/w budesonide with 25 g lactose of 45–63 and 250–355 μm sieve fractions for 2, 5*, 10, 30*, 60 and 120 min (*only 0.4% drug content).

For calculating the coverage of drug particles onto the carrier crystals, some assumptions have been made. It has been assumed that all particles of each kind are spherical and monodisperse with a diameter that equals volume median diameter (X_{50}-value) from laser diffraction analysis

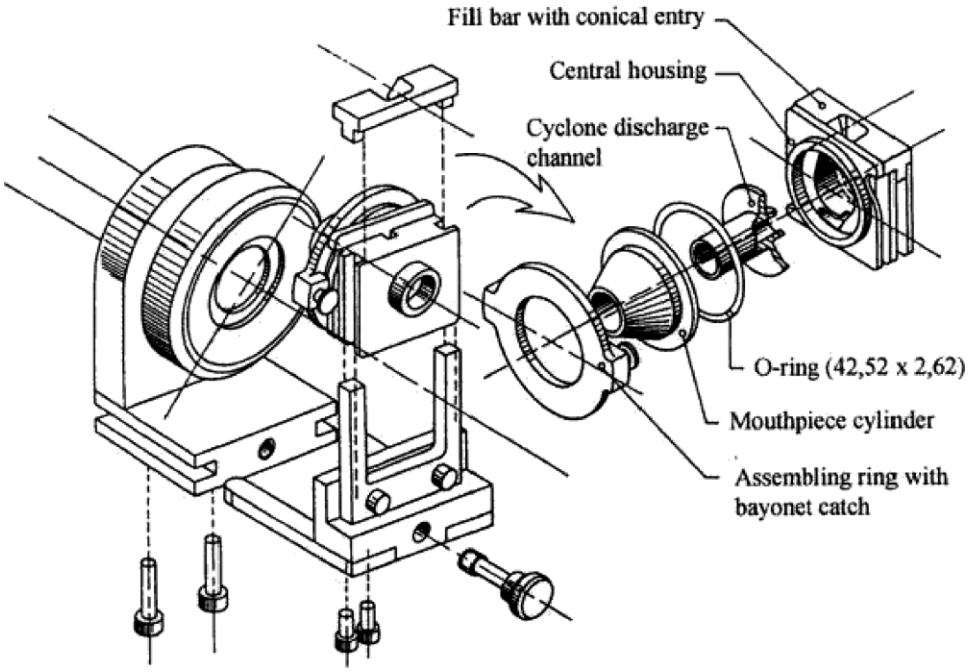

Fig. 1. Test Inhaler (developed and constructed by the University of Groningen, type CV).

for the drug particles and the arithmetic mean of the sieve fraction for the carrier particles, respectively. Furthermore, it was 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 because of non-ideal packing of particles).

Homogeneity was determined for 20 samples of 25 (± 1.0) mg per mixture. The samples were dissolved in 20 ml of solvent (pure ethanol for budesonide mixtures and pure water for dscg mixtures) and the ultraviolet (UV) adsorptions were measured at 243.7 nm for budesonide and 327.6 nm for dscg, using a Philips PU 8720 UV/VIS scanning spectrophotometer (Eindhoven, The Netherlands).

2.4. Cascade impactor analyzes

In vitro deposition of the mixtures was tested with a multi-stage liquid impinger of the Astra type (Erweka, Heusenstamm, Germany), using the induction port as 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 solvent (pure ethanol for budesonide and pure water for dscg), except for the final stage, in which a 76 mm dry glass filter (Gelman Sciences, type A/E, MI, USA) was inserted. Flow rate through the pre-calibrated test inhaler was adjusted to 30 or 60 l/min on the basis of differential pressure measured at the position of the coupling flange.

For the test inhaler, pre-weighted doses of 25 mg were inserted manually. After completion of a series of ten inhalations of 3 s, the drug fractions on the impactor stages were allowed to dissolve for at least 1 h before they were removed for further processing. Prior to UV measurement (at 243.7 nm for budesonide and 327.6 nm for dscg with a Philips PU 8720 UV/VIS), the solutions were clarified by removing non-dissolved lactose particles with a centrifuge (Hettich Rotana, Tuttlingen, Germany) during 5 min rotation at 3000 rpm. Carrier fractions that were retained from the test inhaler after inhalation were treated similarly. The amount of residual drug in these fractions was extrapolated towards 100% retainment and presented as carrier residue (CR). The Fine Particle Fraction is defined as the deposition on the 3rd and 4th stage of the cascade impactor plus the deposition of the glass filter. The theoretical cut-off values of the second stage of the cascade impactor are 12.4 μm (aerodynamic diameter) at 30 l/min and 8.8 μm at 60 l/min. All data given are the mean of two series of ten inhalations.

2.5. Scanning electron microscopy (SEM)

Double-sided adhesive tape was placed on top of an aluminium specimen holder and, after stripping off the protective covering, a small amount of particles was then scattered manually on the tape. The particles were coated with approximately 10–20 nm gold/palladium, using a sputter coater (Balzer AG, type 120B, Balzers, Liechtenstein). SEMs were taken at different magnifications for each sample with a JEOL scanning electron microscope (JEOL, type JSM-6301F, Japan), using an acceleration voltage of 1.5 kV.

3. Results and discussion

3.1. The effect of carrier payload on particle detachment

The volume median diameters obtained from laser diffraction analysis are 1.32 (0.64–2.87) μm for budesonide and 1.73 (0.53–4.28) μm for dscg; the values between the brackets represent the X_{10} and X_{90} values. The relatively low cutpoints of the test inhaler for lactose (19 μm at 60 l/min and 27 μm at 30 l/min, respectively) guarantee that carrier crystals are retained in the test inhaler during inhalation, even for the finest carrier sieve fraction. The uniformity of content had a coefficient of variation below 2.4% for all mixtures used in this study.

Fig. 2 shows the changes in percent CR as function of the carrier payload, at 30 and 60 l/min, for the mixtures with budesonide. The results of the dscg mixtures are not shown, but the same trends were observed. At 30 l/min, the effect of carrier payload on CR is quite different for the three different carrier size fractions. With increasing carrier payload, CR decreases for the finest carrier size fraction (32–45 μm), whereas in contrast, CR for the coarsest carrier size fraction (250–355 μm) shows a clear increase. CR for the intermediate carrier size fraction (150–200 μm) seems to be independent of the amount of drug in the mixture (within the tested range between 0.4 and 6.0%). At 60 l/min the effect is completely different: CR decreases with increasing payload for all three carrier size fractions. The percentage of drug not detached from the carrier crystals at this higher flow rate becomes less than 6.1% for all three carrier size fractions at a payload of 6%. Note that the CR is measured for its relevance to mechanic research of the drug-to-carrier interaction and that the CR can not be used to predict the fine particle fraction. This will be discussed in a next paper.

The differences in the behaviour of the fine and coarse carrier fractions at 30 l/min can be explained by means of the difference in carrier bulk and surface properties of these fractions. For this explanation, initial percent carrier coverage (with drug particles) and both initial and residual amount of drug per unit carrier surface area (mg/m^2) have to be taken into consideration. The carrier residue is only a relative measure, giving no information about the actual carrier payloads before and after inhalation.

For the finest carrier fraction, the theoretical coverage of the carrier particles increases from 4.6 to 69.2% (as percent of a monolayer of drug particles) between 0.4 and 6.0% (w/w) of drug in the mixture. For the coarsest carrier

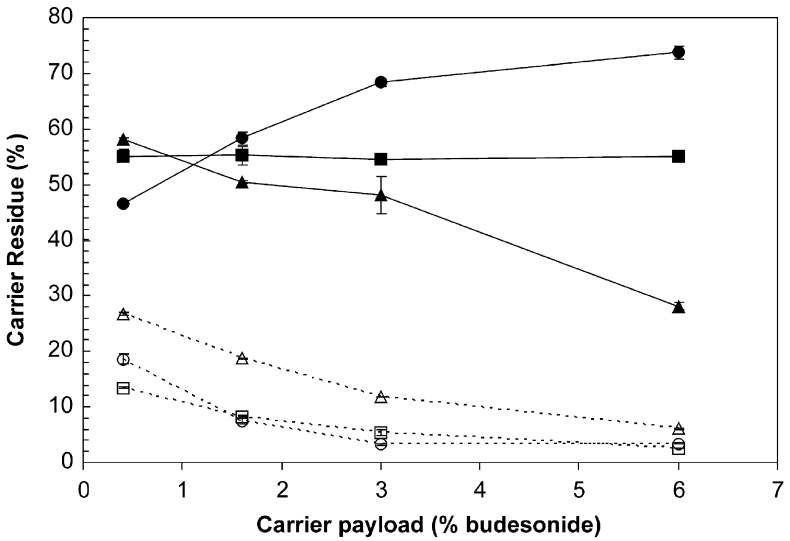

Fig. 2. Carrier residue as function of the carrier payload (% budesonide) from different lactose carrier crystals (△ and ▲ 32–45, □ and ■ 150–200 and ○ and ● 250–355 μm). Closed symbols refer to 30 l/min; open symbols to 60 l/min.

fraction, which has a much lower specific surface area, this increase is much higher from 36.2% (at 0.4% drug) to 543.5% (at 6.0% drug), as shown in Table 1. The residual drug amounts after inhalation per unit carrier surface area are also given in Table 1. They have been derived from the carrier residue values as presented in the table.

The much higher residual payload, at 30 l/min, for the coarsest carrier fraction with 0.4% drug (144.6 mg/m^2) compared to that for the carrier fraction 32–45 μm (23.0 mg/m^2) may be explained by a higher surface rugosity and a much higher initial payload (36.2% theoretical coverage of the carrier surface). Furthermore, a more intensive kneading of the powder during mixing occurs for the coarse fraction. Kneading, during mixing may result in firm pressing of drug particles against the (possible partially ductile layer of impurities on the) carrier crystal surface. Additionally, the formation of drug agglomerates may occur, particularly at higher drug concentrations. Between the different carrier fractions, not only the potential of the active sites (in terms of rugosity) for the larger carrier fraction could be higher, as

Table 1
Carrier residue (%), initial and residual payload of a fine, median and coarse lactose carrier as function of the flow rate

	l/min	Carrier payload (0.4%)	Carrier payload (1.6%)	Carrier payload (3.0%)	Carrier payload (6.0%)	Ratio
Carrier fraction, 32–45 μm						
% Coverage		4.6	18.4	34.6	69.2	
Initial payload (mg/m^2)		39.5	158.1	296.4	592.9	15.0 ×
Carrier residue (%)	30	58.21	50.45	48.16	28.15	
Residual payload (mg/m^2)		23.0	79.8	142.6	166.9	7.3 ×
Carrier residue (%)	60	26.72	18.68	11.91	6.05	
Residual payload (mg/m^2)		10.6	29.5	35.3	35.9	3.4 ×
Carrier fraction, 150–200 μm						
% Coverage		24.0	95.8	179.7	359.3	
Initial payload (mg/m^2)		179.4	717.5	1345.3	2690.6	15.0 ×
Carrier residue (%)	30	55.15	55.22	54.49	55.00	
Residual payload (mg/m^2)		98.9	396.2	733.1	1479.8	15.0 ×
Carrier residue (%)	60	13.45	8.21	5.42	2.61	
Residual payload (mg/m^2)		24.1	58.9	72.9	70.22	2.9 ×
Carrier fraction, 250–355 μm						
% Coverage		36.2	144.9	271.7	543.5	
Initial payload (mg/m^2)		310.1	1240.3	2325.6	4651.2	15 ×
Carrier residue (%)	30	46.62	58.33	68.34	73.70	
Residual payload (mg/m^2)		144.6	723.5	1589.3	3427.9	23.7 ×
Carrier residue (%)	60	18.62	7.57	3.24	3.34	
Residual payload (mg/m^2)		57.7	93.9	75.3	155.4	2.7 ×

shown previously [20]. Also the utilization of these sites is better because of a greater excess of drug particles relative to the number of active sites. Comparison of the residual payloads for the 3.0% drug mixture with carrier fraction 32–45 μm and the 0.4% mixture with the carrier fraction 250–355 μm, both having about the same initial payload of approximately 300 mg/m^2, might lead to the conclusion that the difference in potential for the active sites between these carrier fractions is quite small. For both mixtures, the residual payload after inhalation at 30 l/min is of the same order of magnitude (142.6 and 144.6 mg/m^2) too. Furthermore, this suggests that the effect of kneading during mixing at these respective drug concentrations was not much greater for the coarse carrier fraction than it was for the finest, which is quite reasonable, as will be explained later.

With increasing carrier payload, the differences between the carrier fractions increase. The residual payload increases from 23.0 to 166.9 mg/m^2 for the finest carrier fraction, having a specific surface area of 0.1012 m^2/g, but the increase (7.3 ×) is less than that for the initial payload (15.0 ×), suggesting that the active sites reached their point of saturation. This is quite obvious, considering the percentage carrier coverage reaching a value of 69.2% for the highest drug concentration of 6.0%. For the coarsest carrier fraction with a much lower specific surface area of 0.0129 m^2/g, a certain excess of drug relative to the active sites is likely to be reached already for the lowest drug concentrations (36.2% carrier surface coverage at 0.4% drug and 144.9% at 1.6% drug). Yet, the residual payload (by a factor of 23.7) increases much more with increasing drug content in the mixture than that for the finest carrier fraction. The increase is even higher than that for the initial payload (15.0 ×). For this coarse fraction, the increase in drug concentration changes the interactions in the mixture from drug-to-carrier into predominantly drug-to-drug, since the theoretical carrier coverage increases more than five times the monolayer. Podczeck showed that cohesive forces (between micronized salmeterol particles) are lower than the adhesive forces between lactose and salmeterol, when using the same press-on force [28]. Assuming that budesonide does not show completely different behaviour (in combination with lactose), this suggests that the larger increase in residual payload with increasing initial payload for the coarsest carrier can only have been obtained through extensive kneading of the powder during the mixing process at the higher drug concentrations.

The reason why the effect of kneading increases with increasing carrier payload for the coarser carrier fraction, is explained with the type of rugosity for this carrier fraction. Generally for marketed lactose brands, crystal irregularity increases with increasing crystal size in terms of coalescence and large surface projections. These mostly large scale irregularities of coarse carrier particles have steep faces against which drug particles may accumulate and where they find shelter from press-on forces during the mixing process. Such places are not necessarily active sites where multiple contact points (with the carrier surface) are possible or otherwise increased adhesive forces exists. With increasing carrier payload, the excess of drug particles relative to the places where they can find protection from the press-on forces during mixing decreases and the kneading becomes more important.

At the higher flow rate of 60 l/min, much higher separation forces are generated in the test inhaler, which exceed most of the adhesive (and cohesive) forces in the mixture. Consequently, only a minor fraction of the drug in the mixture is not detached and carrier residues are minimized. Theoretically, the smallest drug particles are not released, as the ratio of removal forces ($F_R \propto d^3$) to adhesive forces ($F_A \propto d$) becomes smaller with decreasing particle diameter d [10]. In practice however, strongly adhering particles (of various sizes) are attached to the active sites. This can be concluded from the found increase in residual payload with increasing percentage of carrier coverage for all three fractions. The increase (2.7 times) between the lowest and highest drug concentration in the mixture at the higher flow rate is smallest for the coarsest carrier fraction, because utilization of the actives sites was already quite complete at the lowest drug concentration. At 60 l/min, the residual payload for the coarsest fraction with 0.4% drug is higher than that for the finest fraction with 3.0% drug (same carrier coverage of approx. 35%) too (57.7 versus 35.3 mg/m^2), which supports the idea that mainly particles attached to actives sites have not been released at the higher flow rate. It has been reported previously that the potential of active sites per unit carrier surface area tends to increase with increasing mean carrier diameter [20].

The given explanation for the observed changes in carrier residue (Fig. 2) can be understood with the help of a previously introduced FDC [10], based on the size distributions of the adhesive and removal forces. Because the generated removal forces are much higher than nearly all adhesive forces at 60 l/min, FDC has only been applied for the situation at 30 l/min. Force size distributions for the fine carrier mixtures are given in Fig. 3; those for the coarse fraction in Fig. 4. In both figures the steepest curves represent the adhesive forces and both other curves (dotted lines) the removal forces (which are proportional to the third power of the drug particle diameter and therefore, exhibit wider (size) distributions).

For the finest carrier fraction, only minor changes in the size distribution for the adhesive forces are expected from an increased drug content in the mixture. An increase in carrier coverage results in a better utilization of the active sites. But it may be expected that the increase in the number of strong adhesive forces for the particles attached to active sites is smaller than the increase in the number of particles attached to non-active sites of the carrier crystal. A slight decrease in the size of the adhesive forces is also likely from a gradual increase in drug-to-drug interactions with increasing carrier payload. And finally, a higher carrier payload results in some drug particle agglomeration due to

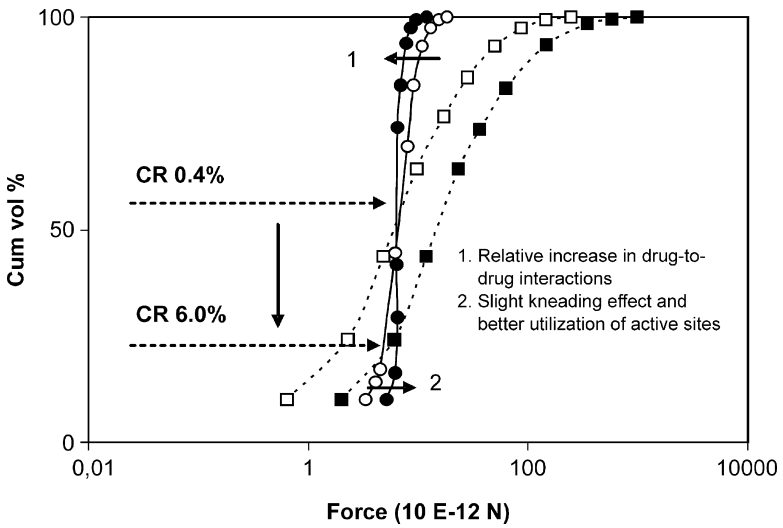

Fig. 3. Application of the FDC to the fine lactose carrier. (□ $F_R(0.4\%)$ = removal forces experienced by the particles in the 0.4% mixture; ○ $F_A(0.4\%)$ = size distribution of adhesive forces for the particles in the 0.4% mixture; ■ $F_R(6.0\%)$ = removal forces experienced by the particles in the 6.0% mixture; ● $F_A(6.0\%)$ = size distribution of adhesive forces for the particles in the 6.0% mixture).

kneading of the particles during the mixing process, although the kneading is not so extreme as for much larger carrier particles. This has been shown previously [42]. The formation of larger drug agglomerates, which is an increase in the size (d) of the particles, increases the adhesive forces ($F_A \propto d$) to a lesser extent than it affects the removal forces ($F_R \propto d^3$).

For the coarsest fraction, changes in the adhesive forces with increasing carrier payload are much more substantial. They result from the high press-on forces occurring during the mixing process (Fig. 4). In addition, drug particles agglomerate into larger clusters, particularly at higher carrier payloads. Therefore, a shift to higher values may also be expected for the removal forces, as particles released as agglomerates have a much higher inertia than primary entities. The release as agglomerates instead of single particles from coarse carrier fraction has been shown previously with the use of laser diffraction technique [42].

Scanning electron microscopy has been applied to support the given explanations. Figs. 5 and 6 show micrographs of the mixtures with 6.0% budesonide for two different carrier fractions (32–45 and 250–355 μm) before and after inhalation at 30 and 60 l/min (for 3 s), respectively. Figs. 5A–C show a clear distinction between the amount of (residual) drug (left) on surface of the fine carrier crystals, before inhalation (592.9 mg/m^2), after inhalation at 30 l/min (166.9 mg/m^2) and 60 l/min

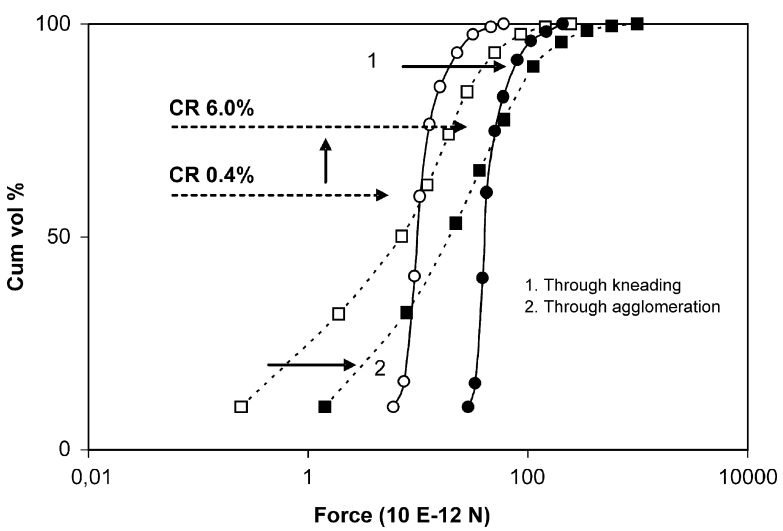

Fig. 4. Application of the FDC to the coarse lactose carrier. (□ $F_R(0.4\%)$ = removal forces experienced by the particles in the 0.4% mixture; ○ $F_A(0.4\%)$ = size distribution of adhesive forces for the particles in the 0.4% mixture; ■ $F_R(6.0\%)$ = removal forces experienced by the particles in the 6.0% mixture; ● $F_A(6.0\%)$ = size distribution of adhesive forces for the particles in the 6.0% mixture).

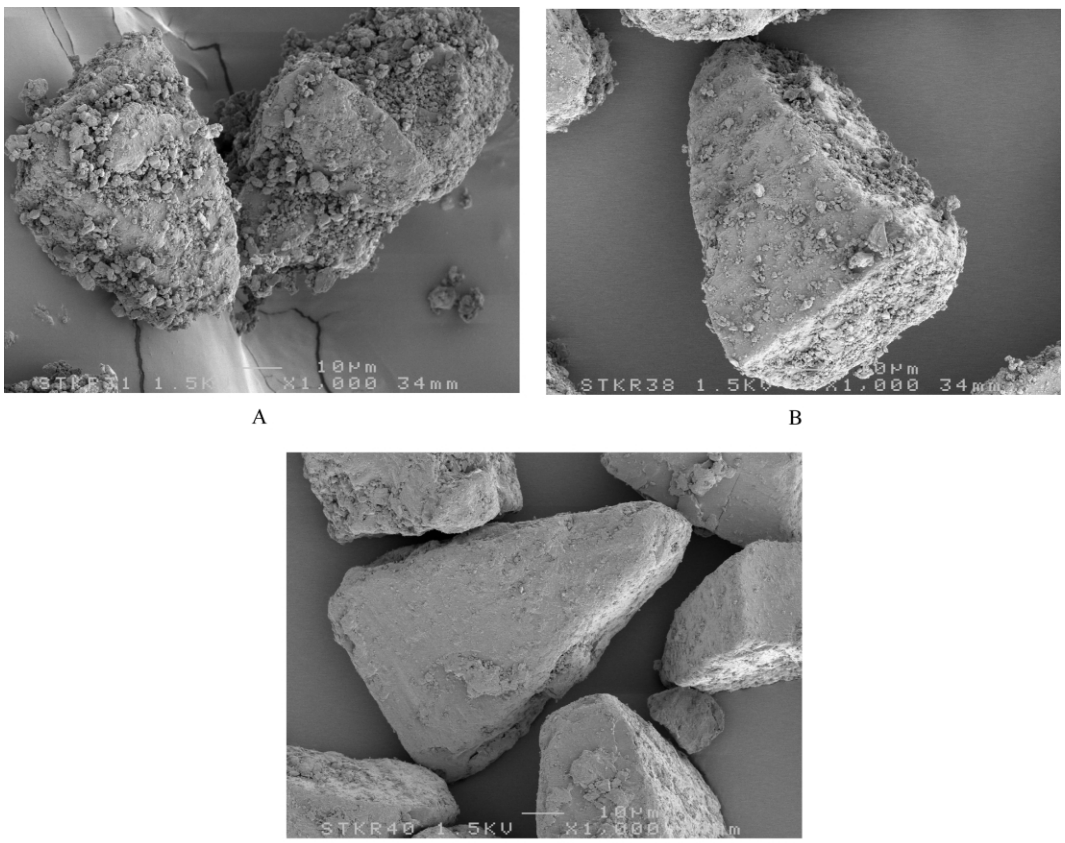

Fig. 5. (A) Fine lactose carrier (32–45 μm) with 6.0% budesonide (w/w), microscopic magnification 1000 × . (B) Fine lactose carrier (32–45 μm) with 6.0% budesonide (w/w) after inhalation at 30 l/min for 3 s in the test inhaler, microscopic magnification 1000 × . (C) Fine lactose carrier (32–45 μm) with 6.0% budesonide (w/w) after inhalation at 60 l/min for 3 s in the test inhaler, microscopic magnification 1000 × .

(35.9 mg/m^2), respectively. In Fig. 6A, the drug theoretically forms a multi-particulate layer around the coarser carrier crystals, which is only partly separated from the carrier crystals at 30 l/min (Fig. 6B), from 4651.2 to 3427.9 mg/m^2. But at 60 l/min the majority of the drug particles is detached, leaving only a small residual payload of 155.4 mg/m^2 (Fig. 6C). For comparison, the initial payload of fraction 250–355 μm with 0.4% budesonide is shown in Fig. 7 at the same magnification. The difference between both figures (Figs. 6C and 7) seems much greater than is expected on the basis of the (residual) drug loads: 155.4 and 310.1 mg/m^2, respectively. The explanation is that the carrier particle in Fig. 6C contains mainly the finest drug particles from the original size distributions, which can hardly be seen at the magnification used. This is a consequence of the decreasing ratio of F_R to F_A with decreasing drug particle diameter, causing predominantly the finer particles to remain attached to the carrier crystals. In Fig. 7 (same magnification) mainly the larger drug particles are seen.

Fig. 7 shows (as in Fig. 6C) that the coarse carrier particles do have irregular surfaces, these clefts and steep slopes of the irregularities give some protection during the mixing and inhalation against press-on and removal forces. The high drug concentration (Fig. 6A) has smoothed [44] the carrier crystal to such a degree that few irregularities can been seen.

3.2. The effect of mixing time on particle detachment

Some additional support for the given explanations (in the previous paragraph) has been obtained from varying the mixing time for a fine and coarse carrier fraction. Using a different budesonide sample ($X_{10} = 0.64$; $X_{50} = 1.31$; $X_{90} = 2.85$ μm) and a different fine carrier fraction (45–63 μm) mixing time experiments were conducted. The carrier residues for mixtures with 0.4 and 4.0% (w/w) drug as function of the mixing time are shown in Fig. 8. Quite remarkable is the difference in carrier residue between the two different budesonide samples used in this study for mixtures prepared at the same mixing time of 10 min (Fig. 2 versus Fig. 8). This, in spite of the fact that both samples have almost the same size distribution. Apparently, drug samples of similar size distributions do not necessarily behave similarly with respect to fine particle re-dispersion during inhalation. We found evidence from SEM observation that the sample used for the mixing time experiments has a greater agglomeration tendency (during mixing) than the sample

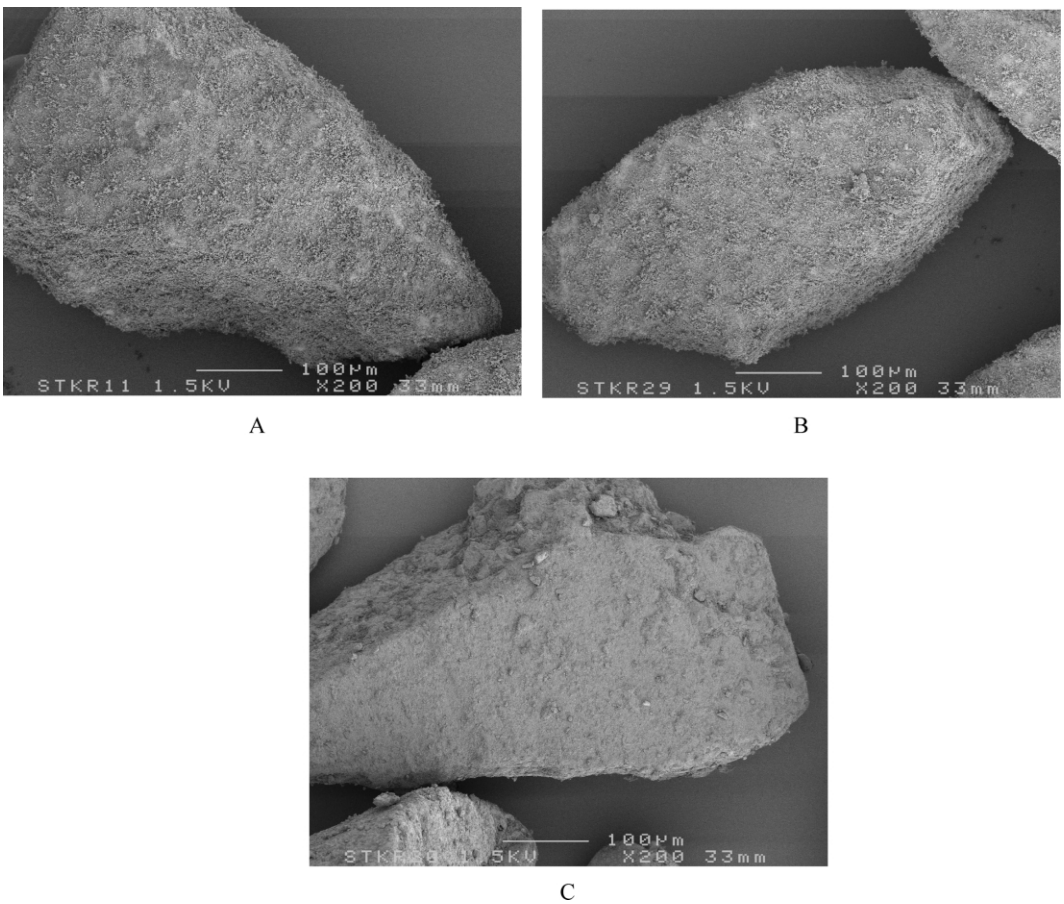

Fig. 6. (A) Coarse lactose carrier (250–355 μm) with 6.0% budesonide (w/w), microscopic magnification 200 ×. (B) Coarse lactose carrier (250–355 μm) with 6.0% budesonide (w/w) after inhalation at 30 l/min for 3 s in the test inhaler, microscopic magnification 200 ×. (C) Coarse lactose carrier (250–355 μm) with 6.0% budesonide (w/w) after inhalation at 60 l/min for 3 s in the test inhaler, microscopic magnification 200 ×.

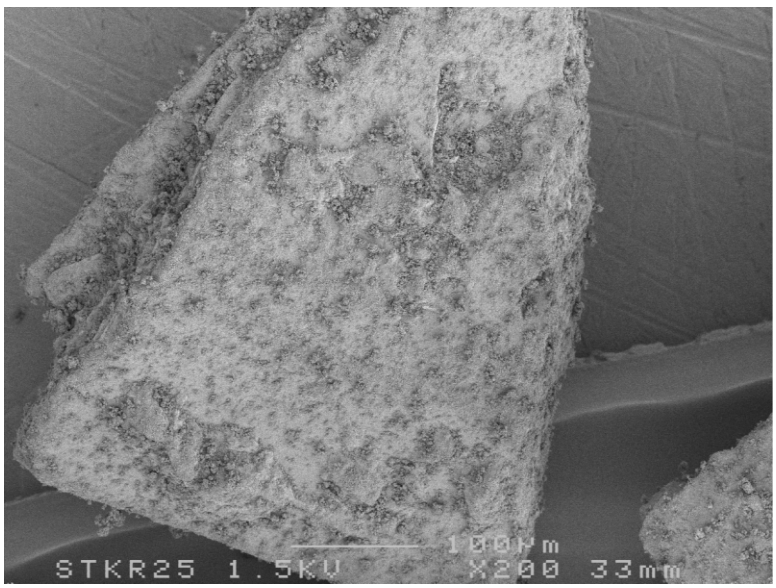

Fig. 7. Coarse lactose carrier (250–355 μm) with 0.4% budesonide (w/w), microscopic magnification 200 ×.

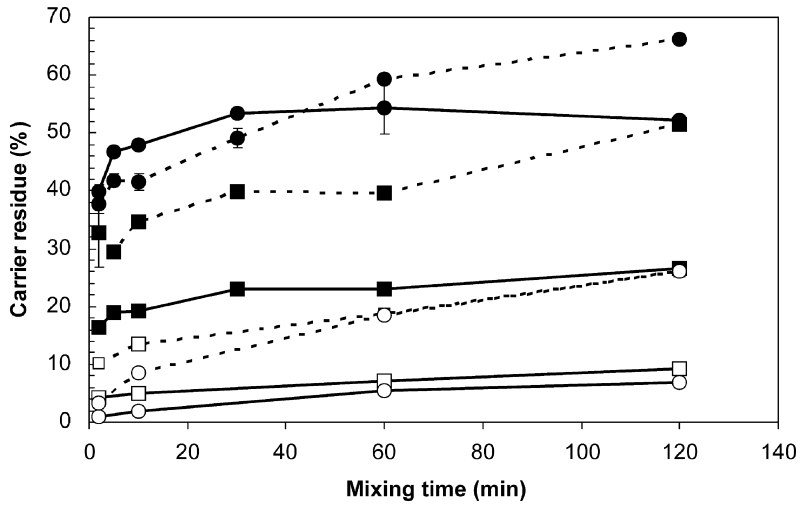

Fig. 8. Carrier residue as function of the mixing time from lactose crystals. (■ and □ 45–63 and ● and ○ 250–355 μm. Closed symbols refer to 30 l/min; open to 60 l/min, dotted lines refer to 0.4% (w/w) budesonide and closed lines to 4.0% (w/w) budesonide).

used for the carrier payload experiments, which increases the size of the removal forces (during inhalation). The reason for this increased agglomeration tendency has not been found yet, but may have been in the micronization process: different comminution conditions and batch-to-batch variation may result in different surface free energies [45–47].

For the mixtures with low drug concentrations, a substantial increase in carrier residue has been obtained with increasing mixing time (from 2 to 120 min): an increase which is larger for the coarse carrier. For the mixtures with 4.0% drug, the increase is also significant, but less extreme and now in reversed order of magnitude (larger for the small carrier fraction). There is also a clear difference in the CR pattern: at low carrier payloads the increase is ongoing between 10 and 120 min mixing time, whereas for the 4.0% mixtures only a minor increase after approximately 30 min mixing time is obtained.

The observed trends seem to agree with the explanations given for the results from the carrier payload experiments. For the coarse carrier fraction at the low carrier payload (0.4%), drug particles can find shelter from press-on forces in the large surface irregularities. Particles accumulate around surface projections, as can be observed with SEM (Fig. 7). However, particles may be detached from such sites by inertial forces during the mixing process and be re-deposited onto places where they become in reach of the press-on forces. This drug re-distribution over the carrier surface seems to continue for a time period of at least 120 min (under conditions as applied).

For the fine carrier fraction, a certain migration from less to more active sites may also be expected, although the surface irregularities are not of the same large scale as those for the much larger carrier particles. In addition, the kneading of the powder is less violent compared to mixtures with coarse carrier fractions, which is the result of the poor flow properties (lower impact and friction forces during mixing). Thus, the pressing of drug particles against the carrier particles, shifting the adhesion forces to a higher value, is a much slower process which is continued up to 120 min mixing time (again, under the applied conditions).

For the coarse carrier fraction, the high drug content of 4.0% equals a theoretical carrier coverage with approximately four monolayers. Therefore, migration of drug particles to sites where press-on forces can be exerted is virtually of no relevance. Instead, kneading of the powder starts from the beginning of the mixing process and has reached its maximum effect after about 30 min under the given conditions. The carrier residue at longer mixing times is lower than that for the 0.4% mixture, because drug-to-drug interactions are predominant (particles attached to the carrier surface with higher adhesive forces are predominantly not detached at 30 l/min).

At 60 l/min, when the removal forces are quite high relative to the adhesive forces, more than 90% of the drug is detached for all mixtures after 2 min mixing time. The quite substantial (relative) increase in CR for the low concentration mixtures with increasing mixing time reflects the firm pressing of the drug particles against the carrier surface after long kneading times.

4. Conclusions

The present results show that the carrier residue (CR) strongly depends on: (a) the size distribution (relevant to the bulk properties of the powder) of the carrier crystals used; (b) the carrier payload; and (c) the mixing time, at lower flow rates through the test inhaler used. It was found that a high carrier payload in combination with coarse carrier crystals is unfavorable due to kneading effects during the mixing process. However, a coarse carrier in combination with a low carrier payload (with a short mixing time) can be

favorable in combination with inhalers generating inertial removal forces, when drug particles are protected in the carrier surface irregularities against press-on forces generated during the mixing process. The detachment of drug particles from small carrier crystals was found to increase with increasing carrier payload (at 30 l/min) due to the low kneading potential of these carrier crystals (poor flowability during the mixing process), while median carrier crystals showed roughly a constant CR with increasing carrier payload. At 60 l/min, the high detachment forces generated in the test inhaler, in relation to the adhesive forces caused the CR of all fractions used to decrease. A negative effect on the drug particle detachment from carrier crystals was found when the mixing time was increased, the CR increased most for the mixtures with the lowest drug content. Thus, the choice of carrier fraction should be made carefully and not only be based on the carrier surface properties; the carrier payload ratio and the bulk properties of the carrier should also be taken into account.

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