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European Journal of Pharmaceutics and Biopharmaceutics 59 (2005) 197–205
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

The interaction between carrier rugosity and carrier payload, and its effect on drug particle redispersion from adhesive mixtures during inhalation

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Received 4 March 2004; accepted in revised form 8 July 2004
Available online 1 September 2004

Abstract

The effectiveness of press-on forces (defined as the adhesive forces between drug and carrier particles) in relation to carrier payload as the result of collisions between carrier particles during the mixing process of an adhesive mixture, has been investigated. Three different carriers of the same size fraction (250–355 μm), but with completely different surface rugosity were studied. It could be shown that this effectiveness depends on the carrier rugosity. The fraction of drug detached from the carrier particles during inhalation appeared to decrease faster with increasing carrier payload for crystalline carriers than for granular carriers. Apparently, increasing the volume of the carrier surface cavities increases the drug mass that can find shelter from the press-on forces during mixing. By measuring the size distribution in the aerosol, it could also be shown that the press-on forces may increase the size of the particles that are detached. This seems to be the result of drug particle re-agglomeration on the carrier surface during mixing. On the other hand, when press-on forces are highly ineffective, an increase in the size of detached particles may also be the result of incomplete break-up of natural drug agglomerates. Finally, it could be shown that when the press-on forces are highly effective, the effect of mixing time is small.

Keywords: Adhesive mixtures; Carrier rugosity; Budesonide; Mixing time; Lactose; Carrier payload

1. Introduction

Micronized drug particles in the size range between 1 and 5 μm for inhalation have poor flow properties, which make reproducible dose measuring and administration difficult. Adhesive mixtures, in which the drug particles are attached to much larger carrier crystals with good flowability, have been described as a suitable type of formulation for inhalation [1,2]. In such mixtures, alpha lactose monohydrate is frequently used as the carrier substance, although the use of other lactose types has been described, like spray dried [3–5] and roller dried (β) lactose [5,6]. It has been recognized that the size distribution [7–10], shape [3,4,11] and surface properties [12–14] of the carrier particles affect the drug-to-carrier interaction. The interaction may also be influenced by carrier payload [7,10] and mixing time [10,15]. Carrier bulk properties are relevant in this respect, as carrier particles apply inertial and frictional (press-on) forces on drug particles attached to their surfaces during mixing when these carrier particles collide with each other and the inner walls of the mixing container [10]. Such press-on forces may increase the adhesive forces in the mixture and decrease the fraction of drug detached during inhalation [16].

Larger particles exhibit better flow properties, and as a result of that, higher forces of impaction during mixing [10]. However, the effectiveness of the press-on forces depends on the carrier payload in relation to the volume of the carrier surface asperities. It has been reported that drug particles tend to accumulate in these asperities [17,18], where they can find shelter from the inertial and frictional press-on forces during mixing. At low payloads when the amount of drug particles is insufficiently high to fill up all the carrier surface discontinuities, the effectivity of the press-on forces is relatively low. Their effect is confined to the drug

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doi:10.1016/j.ejpb.2004.07.005

particles on carrier planes that make contact with each other during mixing. At higher payloads, when the carrier surface discontinuities become saturated with drug particles, more of these drug particles become in reach of the press-on forces. Hence, their effectivity in increasing the adhesive forces is becoming more significant.

Mostly, a high surface rugosity is considered negative for carriers in inhalation mixtures [3,11,17,19,20]. When using an air classifier as de-agglomeration principle, carrier surface discontinuities of a size being much greater than the diameter of the drug particles may be positive, as the inertial separation forces generated in a classifier during inhalation are capable of removing drug particles from these discontinuities. It can be hypothesised that the concentration of drug particles in the mixture finding shelter from the press-on forces in carrier surface asperities, increases when the volume of the asperities is increased. The aim of this study is to obtain proof for this hypothesis. Increasing the volume of the carrier surface asperities has been achieved by granulating smaller (primary) lactose crystals into larger associations with high surface rugosity. The scale of the rugosity has been modified by using different size distributions for the primary particles.

2. Materials and methods

2.1. Starting materials

Pharmatose 80, 100 and 450 M products were supplied by DMV International (Veghel, The Netherlands). 80 and 100 M are coarse and intermediate sized crystalline products, respectively, whereas 450 M is a fine ground crystalline material of which all particles are smaller than 100 μm. Micronized budesonide for inhalation was obtained from Sicor (Milan, Italy), which has a particle size (laser diffraction analysis, dispersed at 3.0 bar) of 1.46 μm as X_{50} (X_{10} is 0.67 μm and X_{90} is 3.20 μm).

2.2. Lactose granulation and preparation of carrier size fractions

Granules were prepared from Pharmatose 100 and 450 M 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 and 3000 rpm, respectively, and after wetting, a kneading phase of 3 min was applied in order to obtain dense and strong aggregates. 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 50 °C for 16 h. Sieve fractions of 250–355 μm were obtained by 30 min vibratory sieving in an Analysette 3 (Fritsch, Idar-Oberstein, Germany) followed by 20 min air jet sieving in an Alpine A200 (Hosokawa Alpine, Augsburg, Germany).

2.3. Characterization of starting materials and carrier size fractions

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 0.5 and 4.0 bar). Lenses of 100 mm (for the drug) and 200 mm (for the carrier fractions) were used and calculations were based on the Fraunhofer theory. All data given, are the mean of two measurements.

The surface texture of the carrier fractions has been expressed with a 'surface roughness index' (SRI), which is the ratio of specific surface area from nitrogen adsorption to calculated surface area. Nitrogen adsorption was performed with a single point BET-apparatus (Quantasorb model QS 14, Quantachrome Instruments, New York, USA), using an 80:20 gas mixture of nitrogen and helium. Samples of approximately 1 g were inserted in test tubes and dried with the gas mixture at 20 °C for 1 h prior to measurement. The calculated surface area has been based on the arithmetic mean of the sieve fraction (302.5 μm), assuming that particles are spherical.

Scanning electron micrographs of the carrier fractions were made with a JEOL JSM-6301F microscope (JEOL, Tokyo, Japan), using an acceleration voltage of 1.5 kV. Particles were scattered on double-sided adhesive tape on top of an aluminium specimen holder and subsequently coated with approximately 10–20 nm of gold/palladium, using a Balzers 120B sputter coater (Balzers AG, Liechtenstein).

2.4. Adhesive mixture preparation and characterization

All three carrier types were mixed with 0.4; 1.0; 2.0; 4.0 and 8.0% (w/w) budesonide, respectively, in a batch size of 25 g, using a tumbling mixer Turbula T2C (WA Bachofen, Basel, Switzerland) at 90 rpm. To minimize the effects of tribocharge, a 160×10^{-4} m^3 stainless steel container was used. Mixing time was 10 min, but for mixtures with 0.4 and 4.0% (w/w) budesonide also a mixing time of 60 min was applied.

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

Scanning electron micrographs of the mixtures were made according to the procedure as described for the carrier size fractions.

2.5. Test inhaler and carrier residue

The special test inhaler used for the inhalation experiments has been described previously [10]. This test inhaler has an air classifier as powder de-agglomeration principle

with carrier retention. Individual doses of 25 mg were weighed and inserted manually and retained carrier particles were analyzed on residual drug, using the same procedures as described for homogeneity testing of prepared mixtures. Residual drug was expressed as percent of initial drug content in the mixture and corrected (if necessary) for minor carrier passage through the classifier by linear extrapolation to 100% retention, and is referred to as carrier residue (CR). Inhalation experiments were either performed with a cascade impactor or with laser diffraction technique as described hereafter.

2.6. Laser diffraction analysis of the aerosol cloud

Particle size analysis of 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 [21]. 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 or 30 l/min, respectively. Each value presented, is the mean of 10 measurements and for each individual measurement a reference measurement was performed on the carrier without drug, in order to make corrections for released lactose fines.

2.7. Cascade impactor analyses (CIA)

The aerodynamic size distribution of the aerosol from the test inhaler was tested with a Multi-Stage Liquid Impinger (MSLI) 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 ethanol p.a., except for the final stage, in which a 76 mm dry glass filer (Pall Corporation, type A/E, Michigan, 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 and the inhalation time was 3 s.

After completion of a series of 10 inhalations, the drug fractions on the impactor stages were allowed to dissolve for at least 1 h, before they were collected. Processing of the drug solutions was the same as described for homogeneity testing. Fractions derived from the stages 2 to 4 and the filter were used to calculate fine particle fractions smaller than 5 μm. Experimental cut points for the second stage of the MSLI have been calculated on the basis of the equations given by the European Pharmacopoeia 4th Ed. All results are the mean of two series of 10 inhalations each. The experiments were carried out at 19 ± 1 °C and 46 ± 6% relative humidity.

3. Results and discussion

3.1. Physical properties of the starting materials

Table 1 summarizes the results from characterization of the lactose carrier types. The X_{50}-values from laser diffraction analysis (0.5 bar dispersion pressure), which may be considered as volume median diameters (VMDs), are slightly different and do not all match the arithmetic mean (302.5 μm) of the sieve fraction. This is a result of a difference in particle shape, which is wedge-like for the crystals, and more or less spherical for the granules. The granules have a higher SRI than the crystals. As expected, the SRI-value of the 450 M granules is much higher than that of the 100 M granules. This may be explained by the difference in primary particle size of the starting materials.

An indication for the strength of the granules was obtained from dispersing the granule fractions at two different pressures (0.5 and 4.0 bar) with the RODOS dry powder disperser. Fig. 1 shows the size distributions of both types at both pressures in comparison with those for the starting materials Pharmatose 100 and 450 M (at 0.5 bar). The differences in result from different dispersion pressures are quite small, indicating that the granules are strong and able to withstand the relatively mild forces during the mixing and inhalation processes.

3.2. Effect of carrier payload on the carrier residue

The mixtures prepared, exhibited good homogeneities; all variation coefficients were smaller than 1.8%. The effect of carrier payload on the CR is shown in Fig. 2 for the two different flow rates. At both flow rates, the trend for the coarse crystalline carrier type is the same as reported previously [10], in spite of the fact that different lactose and budesonide batches were used. At the lower flow rate of 30 l/min, CR increases with increasing payload. As explained previously [10], a payload of 0.4% already corresponds (theoretically) with 36.2% coverage of the carrier crystals with drug particles. A further increase in payload results in an excess of drug particles relative to places where these particles can find shelter from the press-on forces during mixing. Consequently, the adhesive forces in the mixture can be increased.

Table 1
Physical properties of the lactose carriers

	X_{10} (μm)	X_{50} (μm)	X_{90} (μm)	BET (m^2/g)	SRI
80 M crystals (250–355 μm)	244.7	352.5	467.4	0.112	8.68
100 M granules (250–355 μm)	188.9	309.1	433.5	0.147	11.40
450 M granules (250–355 μm)	236.7	339.9	467.2	0.323	25.04

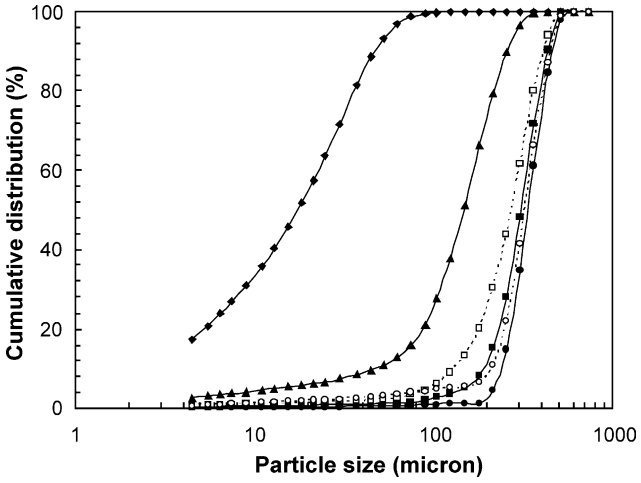


Fig. 1. Particle size distributions of 100 and 450 M granules versus their primary particles and their break-up in a RODOS dispenser with increasing pressure (0.5–4.0 bar), $n=2$. (▲ 100 M primary particles, ♦ 450 M primary particles; ■ and □ 100 M granules and ● and ○ 450 M granules. Closed symbols refer to 0.5 bar; open symbols to 4.0 bar).

For the granular carrier types, having large surface cavities (Fig. 3), a larger amount of particles finds shelter from press-on forces during the mixing process. Therefore, as expected, carrier payloads at which the CR starts to increase, are higher than for the crystalline carrier of the same size fraction (80 M: 0.4%; granular 100 M: ±1%; granular 450 M: ±2%). The difference in CR between the 100 and 450 M granules is an interesting phenomenon. It shows that the size and efficacy of press-on forces during the mixing process not only depends on carrier size distribution and carrier payload, relative to the sheltering capacity of the carrier surface irregularities, but also to the scale of the rugosity. Which has to be considered in relation to the type of mixer used. If the carrier discontinuities are quite large (as for the 100 M granules), large drug agglomerates can be stored

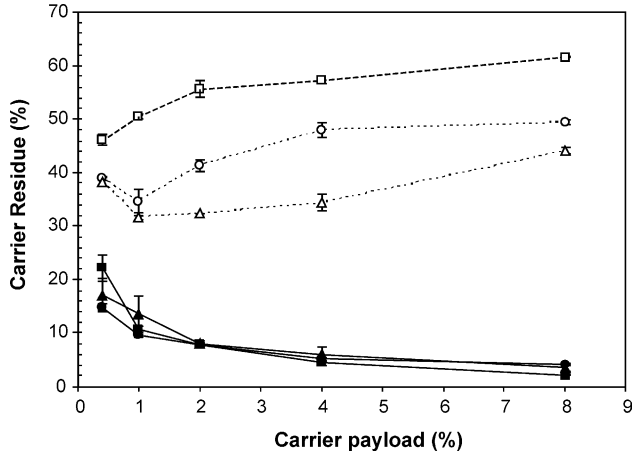
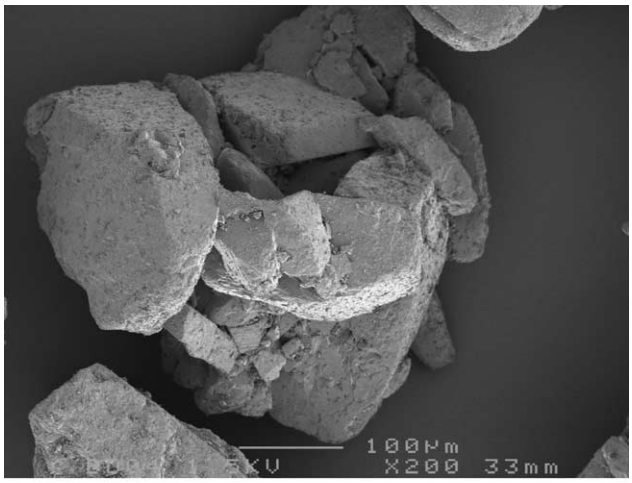


Fig. 2. Carrier residue as function of the carrier payload (%) at 30 l/min (open symbols) and 60 l/min (closed symbols) (3 s) with the test inhaler CV, □ and ■ refer to 80 M lactose crystals (250–355 μm), ○ and ● to granules made from 100 M lactose (250–355 μm), △ and ▲ to granules made from 450 M lactose (250–355 μm).



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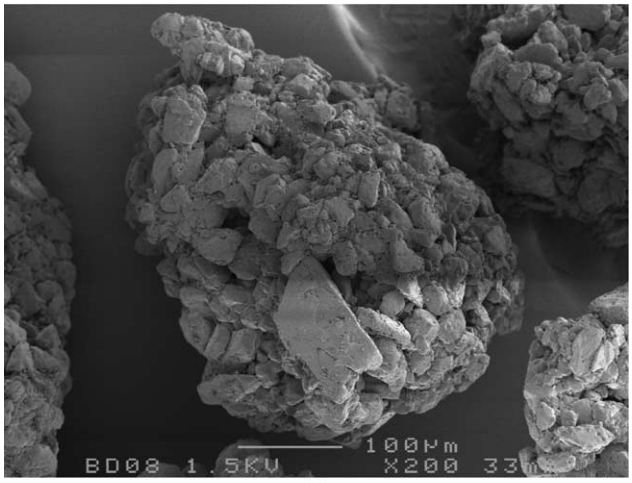


B

Fig. 3. SEM pictures of granular lactose types (A) 100 M granule (250–355 μm) and (B) 450 M granule (250–355 μm), microscopic magnification 200×.

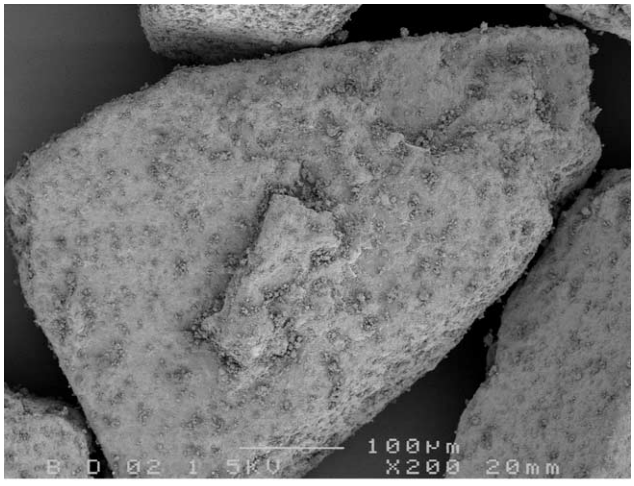
in the cavities, but also relative large crystal planes are available at the periphery of the granules, as shown in Fig. 3A. In a tumbling mixer of the Turbula type, relatively large impact forces are generated, as the powder is thrown quite violently to and fro. Particularly, if the mixing container has a low filling degree, as in our studies. Large drug agglomerates in the large carrier cavities are subjected to high inertial forces that may remove these agglomerates from the cavities for further distribution over the carrier surface. Break-up into smaller drug agglomerates and distribution over the (peripheral) crystal planes results in a greater exposure to the press-on forces. Also, because the extremities on the 100 M granules are most likely capable of reaching a part of the drug particles in the larger surface cavities during collisions. In the much smaller cavities of the 450 M granules (Fig. 3B), smaller drug agglomerates can be stowed away and inertial forces acting on these agglomerates during the mixing process are much lower. Therefore, re-distribution during the mixing process is less extreme, whereas there are no extremities and large surface planes on the periphery of

the granules. The initial decrease in CR (from 0.4 to 1.0% payload) can be explained by an increasing number of drug particles relative to the capacity of strong bonding sites on the individual crystal planes of the 100 and 450 M particles [10].

At the higher flow rate of 60 l/min, the removal forces in the classifier are so high, relative to the adhesive forces, that nearly all particles are detached. The increase with decreasing carrier payload at this flow rate is the result of an increasing number of strong bonding sites relative to the number of drug particles attached to the carrier surface. Only particles attached to such sites and the finest particles in the drug sample are not released during inhalation. The differences in degree of drug detachment between the carrier types at this higher flow rate are negligible, except for the lowest payload which probably reflect the differences in capacity of strong bonding sites between the starting materials.

SEM micrographs (Fig. 4) seem to support the hypothesis made regarding the difference in behaviour of the different carrier materials. Fig. 4A shows the crystalline carrier fraction at low payload. Most of the drug particles are accumulated against steep faces of surface projections, as reported previously [17,18]. Here, bonding forces may be somewhat higher (e.g. as the result of multiple contact points), but drug particles also find shelter from press-on forces during the mixing process. At higher payload (Fig. 4B), sheltering capacity is insufficient and particles are distributed over the total carrier surface.

Fig. 5A shows a 100 M granule with 4.0% (w/w) payload. A fraction of the drug is accumulated in the rather deep cavities between the primary particles. Another fraction is distributed over the relatively large crystal planes of the primary particles. This supports the previously given explanation that inertial impaction forces during mixing may remove part of the drug agglomerates from the cavities for redistribution over the surface of the primary particles. Particularly on the large peripheral planes, drug particles are



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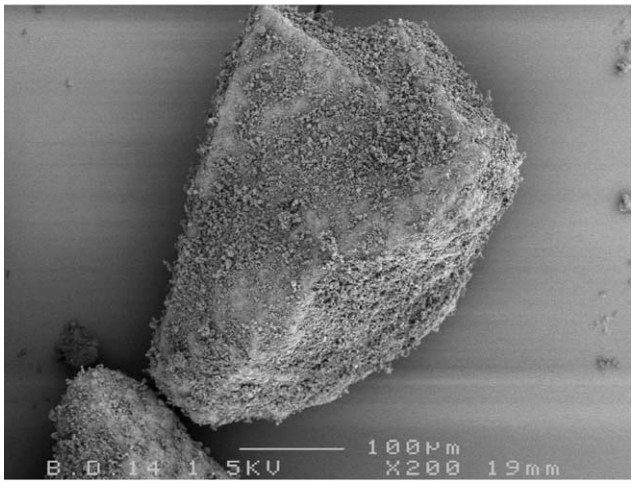
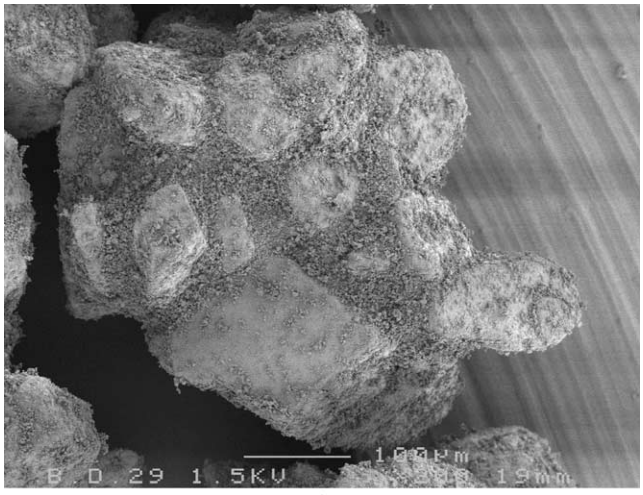


B

Fig. 4. SEM pictures of crystalline lactose loaded with budesonide. (A): 80 M (250–355 μm) with 0.4% budesonide (w/w) and (B): 80 M (250–355 μm) with 4.0% budesonide (w/w), microscopic magnification 200×.



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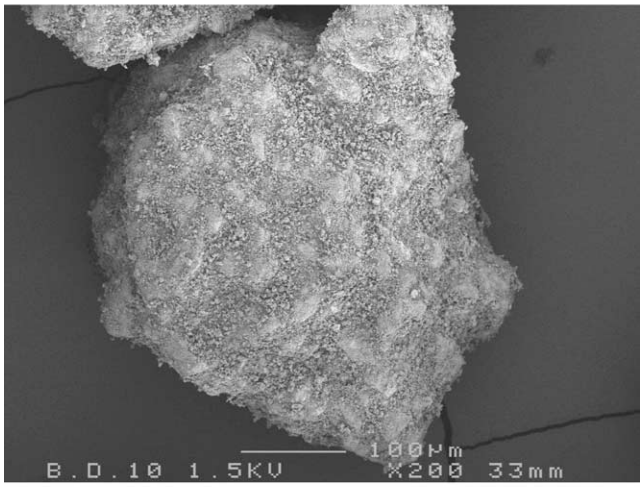

B

Fig. 5. SEM pictures of granular lactose loaded with budesonide. (A) 100 M granule (250–355 μm) with 4.0% budesonide (w/w) and (B) 450 M granule (250–355 μm) with 4.0% budesonide (w/w), microscopic magnification 200×.

in reach of the press-on forces. Fig. 5B shows that the drug distribution over the surface and cavities of the 450 M granule is basically the same as that over the 100 M granule. The difference between both granules is the size of the cavities between the primary particles and the overall shape of the particle. Primary 450 M particles do not stick out from the granule surface and seem unable to penetrate into the pores between the primary particles of the granules with which they collide during mixing (Fig. 3B). Therefore, the effectivity of the press-on forces is quite low. Fig. 5B shows that most strongly protruding parts of these primary particles are rather free from adhering drug particles. These seem to be the parts that make contact when carrier particles collide with each other.

3.3. The size of detached drug particles

Normally, the mass fraction and size distribution of detached drug particles is studied with CIA. We used laser diffraction technique for two reasons. It has been reported previously [22] that an air classifier exhibits a 2-step de-agglomeration. Particles may be detached as small agglomerates and be further disrupted into primary entities before they are discharged from the classifier. Therefore, the mode of detachment, particularly at higher flow rates cannot be studied. Cascade impactors cannot be operated at extremely low flow rates (e.g. 10 l/min) however, because of their large volumes (decreasing the flow increase rate through the test inhaler and by that, the performance of the inhaler) and also because carrier particles deposit in the induction port. Besides, cascade impactors classify upon aerodynamic diameter, as a consequence of which it is difficult to discriminate between large single entities (with high density) and agglomerates (with low density), possibly having approximately the same aerodynamic size.

Fig. 6 shows the mean (geometric) diameter of detached drug particles from all three carrier types (five different payloads) at 10, 20 and 30 l/min, respectively. The results at lowest inspiratory flow rate (low detachment forces) suggest that detached particles are a mixture of the largest primary entities and small agglomerates. This is the same for all carrier fractions. The X_{50}-values varying from approximately 3–5 μm are clearly higher than the X_{50}-value for the drug from RODOS dispersion (1.46 μm). This may not be surprising as the SEM micrographs show that most drug particles are not attached to the carrier surface as single entities, whereas removal forces in a classifier are highest for the largest drug particles, as has been explained with a previously introduced force distribution concept [22]. For the crystalline carrier fraction, the mean size of the released particles increases with increasing carrier payload. This is in agreement with previous observations that drug particles tend to form agglomerates on the carrier surface [18]. The higher degree of agglomeration at a higher carrier payload, confirms the increasing efficiency of press-on forces during mixing with increasing payload [10].

For the granular carriers there is no increase in X_{50}, but there is an interesting difference between the 100 and 450 M granules; the latter showing a decreasing X_{50}-value with increasing payload at 10 l/min, which is an opposite trend as found for the crystalline carrier fraction. To explain this, it should be realized that the drug contains 'natural agglomerates' which are the reason why screening of the drug through a sieve prior to mixture preparation is a standard procedure. Without screening, the relatively hard agglomerates cannot be broken sufficiently during

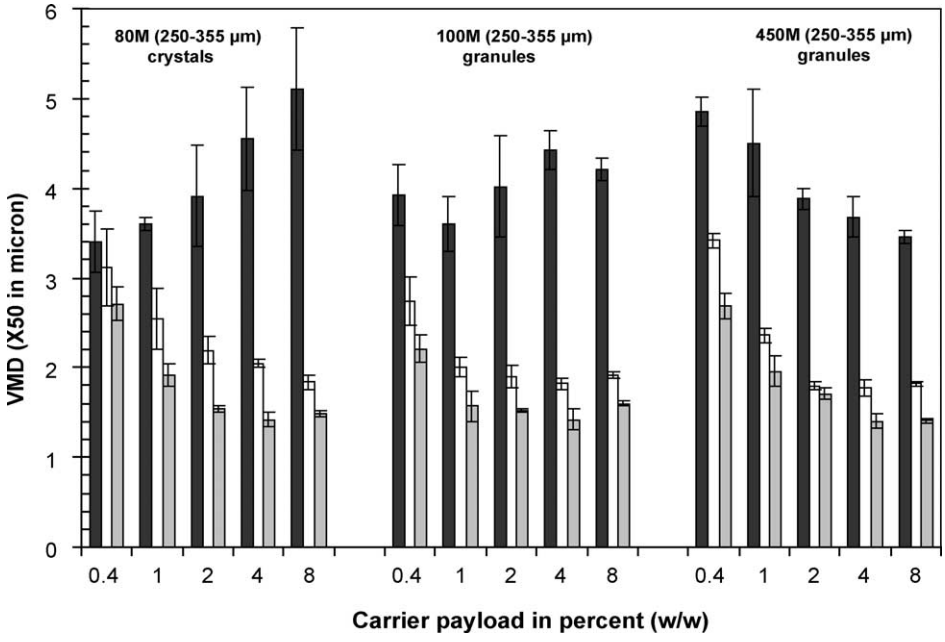

Fig. 6. Volume median diameter (VMD) (×50 in micron) as function of the carrier payload (% w/w) and flow rate (l/min), $n = 10$ (dark columns refer to 10 l/min; open columns refer to 20 l/min; medium-coloured columns refer to 30 l/min, inhalation time is 3 s).

the mixing process and a poor mixture homogeneity is obtained. However, small agglomerates are not disintegrated, as the aperture of the sieve is generally much higher than the primary drug particle size. Such agglomerates have to be broken up during the mixing process [23,24], for which the same forces are responsible as for pressing the drug particles firmly to each other and to the carrier surface. It seems evident, that when press-on forces are low (e.g. for 450 M granules at low payload), fine particle break-up during mixing is incomplete, resulting in attachment of relatively large agglomerates to the carrier particles. During inhalation (at lower flow rates) such agglomerates are released as a whole and not further de-agglomerated into finer particles.

Increasing the flow rate has the same effect for all carrier types (Fig. 6), smaller particles are detached, and detached agglomerates are further de-agglomerated by the classifier into primary entities. As a result, the X_{50}-value decreases with increasing flow rate. The decrease in X_{50} with increasing carrier payload for all carrier types at higher flow rate, can be explained similarly as above for the 450 M carrier at 10 l/min. At low payload, fine particle break-up during the mixing process is incomplete, which results in detachment of small agglomerates rather than that of primary drug particles. The mean primary drug particle size (X_{50}-value) in the aerosol at 30 l/min at higher carrier payloads is only slightly higher than that for the starting material obtained with RODOS dispersion. Most likely the smallest drug particles, subjected to the lowest removal forces, may not be detached from the carrier crystals, which increases the median diameter of the aerosol. Whereas de-agglomeration of detached small agglomerates in the classifier may not have been complete. This aspect will be further investigated in a follow-up study.

3.4. The effect of mixing time on carrier residue

Previously, it has been shown for crystalline carrier fractions that increasing the mixing time increases CR, which is the result of sustaining the action of press-on forces during the mixing process [10]. The increase in CR with increasing mixing time was largest when the size, or effectiveness, of press-on forces was lowest. The same trend is found for the mixtures with coarse carrier types in this study (Fig. 7). At low carrier payload, when drug particles can find shelter in carrier surface irregularities, it requires time to relocate these drug particles onto sites where the press-on forces can be effective. Particularly, because the drug agglomerates on crystalline carriers at low payload are relatively small (Fig. 6), as a result of which the inertial forces that are necessary for relocation are small too. This is also true for the granular carriers, for which the cavities are even larger. Drug agglomerates may be slightly larger (as suggested by Fig. 6), but the total surface area accessible to press-on forces is lower than that for a crystalline carrier of the same size. At higher payload, relocation for the coarse crystalline carrier is not of interest, because there exists a multilayer of drug around the carrier particles. The size and the effectiveness of the press-on forces are high, and maximal adhesive (and cohesive) forces have already been established after 10 min mixing time. For granular carriers, the size of the press-on forces is the same as that for the crystalline carrier of the same size fraction, but the effectiveness is lower, as shown in Fig. 6. Granules prepared from finer particles contain smaller cavities, which

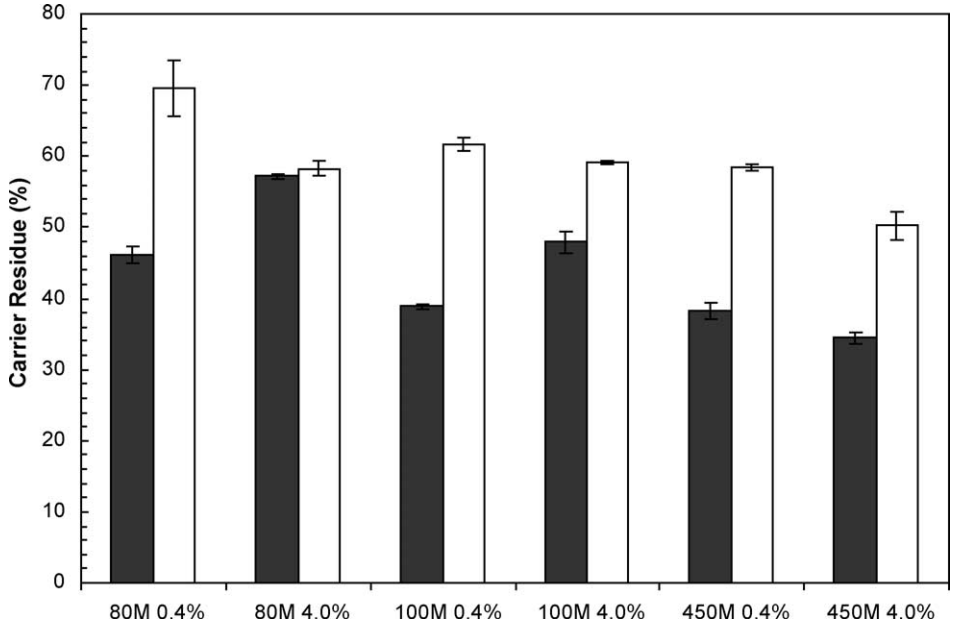

Fig. 7. Carrier residue (%) as function of the mixing time. Open columns refer to the CR values after 10 min of mixing, dark columns refer to the CR values after 60 min of mixing.

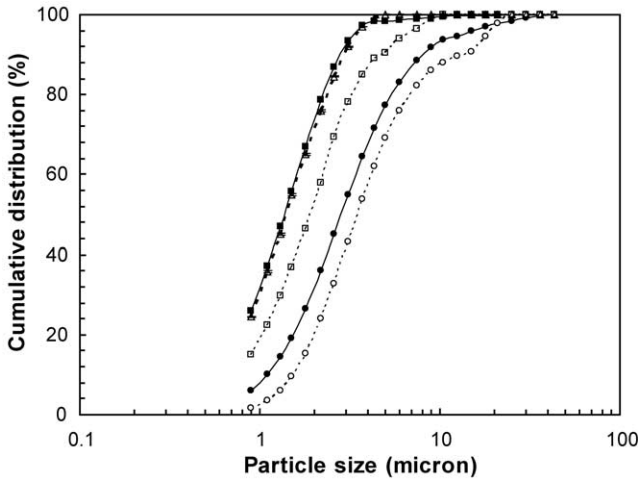

Fig. 8. Size distribution in the aerosol from mixtures containing crystalline (80 M) carrier fraction 250–355 μm with two different payloads (○, ● 0.4 and □, ■ 4.0%). The mixtures were prepared using 10 min (closed) and 60 min (open symbols) mixing time. Inhalation at 30 l/min (3 s), Δ represent the primary particle size of budesonide from RODOS dispersion (at 3.0 bar).

contain smaller drug agglomerates, onto which smaller relocation forces act during the mixture process, whereas such granules also have a lower ratio of surface area accessible to press-on forces to total surface area. Consequently, the effect of mixing time at higher payload is larger for 450 M than for 100 M granules.

A longer mixing time also increases the size of the released particles (Fig. 8). As in Fig. 6 (at 30 l/min), the X_{50}-value in the aerosol is lowest for the highest carrier payload. But although in Fig. 7 an increase in mixing time does not seem to increase the CR for the coarse crystalline carrier at 4.0% payload, it does affect the size of the particles that are released at this relatively low flow rate. Fig. 8 also shows the primary size distribution of the drug from RODOS dispersion, which is nearly the same as that in the aerosol from the test inhaler for the mixture with 4.0% budesonide (after 10 min mixing time).

4. Conclusions

Bulk properties may be as relevant to the adhesion between drug and carrier particles as carrier surface properties [10]. As a result of inertial and frictional press-on forces during mixing, adhesive and cohesive forces in the mixture may be increased, which reduces the fraction of drug detached during inhalation. The size of the press-on forces was found to increase with the mean carrier diameter (mass), whereas their effectivity increases with the carrier payload. At low payload, carrier surface discontinuities (in which drug particles tend to accumulate) provide shelter from these forces. In this study, it has been shown that increasing the scale of the carrier rugosity increases the sheltering capacity from these forces. As a result, the payload at which the detached fraction of drug (during inhalation) starts to fall of can be increased. An increase in macroscale rugosity can be obtained from granulating fine or intermediate sized lactose particles. The size of the carrier surface pores and the shape of the granules appear to be important. Drug agglomerates may also be removed from large pores by inertial forces during mixing. This causes relocation of drug particles on large crystal planes of primary particles where they become in reach of the press-on forces. The extent to which this occurs depends on the mixing time. Smaller pores and rounded granules seem to be more effective. It has been shown that the drug particles are at least partly detached as small agglomerates during inhalation. Agglomeration on the surface has been reported before [18], but it has never been shown that the size of the agglomerates increases with the size and effectivity of the press-on forces. Nor has it been discussed before that the press-on forces seem also responsible for the break-up of natural agglomerates during mixing.

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