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The effect of carrier surface treatment on drug particle detachment from crystalline carriers in adhesive mixtures for inhalation

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Abstract

In this study, the effect of lactose carrier surface treatment on drug particle detachment during inhalation has been investigated. Crystals of marketed brands of alpha lactose monohydrate brands normally exhibit a certain surface rugosity and contain natural fines and impurities on their surface, which influence the drug-to-carrier interaction in adhesive mixtures for inhalation. Submersion treatment may change these surface characteristics. Two different sieve fractions (63–90 and 250–355 μm) were submerged in mixtures of ethanol and water (96 and 80% v/v, respectively). Microscopic observation and laser diffraction analysis revealed that neither the shape nor the size of the carrier particles was changed by the submersion treatment. However, the specific surface area and the amount of impurities appeared to decrease substantially after submersion, and the magnitude of the decrease was different for the different ethanol–water mixtures. The reduction in specific surface area was attributed particularly to the removal of the adhering lactose fines from the carrier surface. Mixtures with budesonide (in a wide range of carrier payloads) were prepared before and after treatment. Drug particle detachment from the various mixtures was studied with a sieve test and with a cascade impactor analysis at 30 and 60 l/min. Two different types of inhalers were used, one generating lift- and drag-forces (ISF inhaler) and one generating inertial forces (test inhaler), respectively. The cascade impactor and sieve test experiments showed that an increase in carrier surface smoothness results in a reduced drug particle detachment during inhalation, which was independent of the type of inhaler used. This reduction could be attributed to the removal of the adhering lactose fines which may provide shelter for the drug particles from press-on forces during mixing.

Keywords: Adhesion; Budesonide; Carrier lactose; Dry powder inhaler; Surface treatment; Rugosity

1. Introduction

In adhesive mixtures for inhalation, micronized drug particles are distributed homogeneously over the surface of much larger carrier particles, commonly crystalline alpha lactose monohydrate particles. The interaction forces between drug and carrier surface are predominately Van der Waals' forces, but also electrostatic (coulombic) and capillary forces may play a role (Visser, 1989; Hickey et al., 1994). It has been recognized that the drug distribution and the drug-to-carrier interaction are influenced by the carrier payload (Steckel and Müller, 1997; Dickhoff et al., 2003), the mixing time (Zeng et al., 2000b), the mixing intensity (Dickhoff et al., submitted), the carrier surface (de Boer et al., 2003) and bulk properties (Timsina et al., 1994; Dickhoff et al., 2003). The carrier size distribution is relevant to both latter aspects (Kulvanich and Stewart, 1987; Podczeck, 1999). Large carrier particles exhibit relatively high inertial and frictional press-on forces during mixing. These press-on forces have the potential to increase the adhesive forces in the mixture, depending upon the carrier payload (Dickhoff et al., 2003, 2005). Larger carrier particles also have higher surface rugosities (Kawashima et al., 1998; Dickhoff et al., 2003) and more surface impurities (de Boer et al., 2003) both may affect the type and intensity of the interaction between drug and carrier. Therefore, controlling the carrier surface properties has been the objective of many studies. For instance, different techniques have been applied to reduce the carrier surface roughness. These techniques include crystallization from Carbopol gels (Zeng et al., 2001a), coating with isoleucine or magnesium stearate (Colombo et al., 2000; Young et al., 2002), temperature controlled etching (El-Sabawi et al.,

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2004) or surface treatment of the carrier crystals by submersion in (or wetting with) ethanol solutions (Zeng et al., 2001b; Iida et al., 2003). In the majority of these studies, an increased fine particle fraction during inhalation has been obtained with increasing carrier smoothness (Colombo et al., 2000; Zeng et al., 2000a; Iida et al., 2003). This has been attributed to a reduction of the binding sites with multiple contact points (Kassem and Ganderton, 1990; Podczeck, 1998). However, there are also studies in which a reduction of the carrier surface discontinuities has resulted in lower fine particle fractions (Zeng et al., 2001b). The result was explained by the removal of microscopic surface irregularities, which increases the contact area of a single contact point between a drug and carrier particle (Podczeck, 1999; Price et al., 2002).

The conflicting results seem to point in the direction of an optimal surface rugosity (Heng et al., 2000). Only when the size of the carrier surface irregularities is at a scale that reduces the total contact area of a single contact point between a drug and carrier particle, does it reduce the adhesive interaction force. When the size of the irregularities is either larger or approaches zero, it may increase the adhesive force. The difference in obtained effect could also be the result of different circumstances during the (inhalation) experiments however, for example, it has been shown that a high carrier rugosity reduces the fine particle fraction during inhalation when turbulent shear inhalers are used (Heng et al., 2000; Zeng et al., 2000a). But when the powders are dispersed with an inhaler that generates inertial separation forces, a high rugosity may be advantageous, particularly at payloads below saturation point of the carrier surface cavities inside which drug particles may find shelter from press-on forces during the mixing process. However, this depends on the mixing intensity too (Dickhoff et al., submitted).

The aim of this study was to investigate through which mechanism carrier surface treatment affects drug particle detachment during inhalation. This was evaluated using an experimental design to assess the influence of the following variables on the detachment process. Two different carrier size fractions (63–90 and 250–355 μm) were used both untreated and both after submersion in 96% v/v ethanol and submersion in 80% v/v ethanol, respectively. Mixtures were prepared with 0.4; 1.0; 2.0 and 4.0% w/w of budesonide, using untreated and treated carrier fractions. Drug detachment was tested with two different inhaler types: ISF inhaler (de-agglomeration through turbulent shear) and a special test inhaler (de-agglomeration through inertial impaction in an air classifier principle) at two different flow rates of 30 and 60 l/min. Drug detachment rate was also studied with an air jet sieve.

2. Materials and methods

2.1. Starting materials

Micronized budesonide (supplied by Sicor, Milan, Italy) in a size distribution 10% <0.60 μm and 100% <2.69 μm (X_{50} = 1.42 μm from dry laser diffraction analysis) was used as drug. Carrier size fractions were derived from Pharmatose 80M (DMV International, Veghel, The Netherlands).

2.2. Preparation of carrier lactose

Carrier fractions 63–90 and 250–355 μm were prepared by 30 min vibratory sieving (Fritsch Analysette 3, Germany) followed by 20 min of air jet sieving (Alpine A200, Augsburg, Germany). Part of the lactose sieve fractions was treated with aqueous ethanol solutions with 96 and 80% (v/v) ethanol respectively, to remove impurities and adhering fines from the particle surfaces and to reduce the surface irregularities in order to produce carrier crystals with increased surface smoothness. For this treatment, 200 g of lactose particles was added to 2 l of one of the aqueous ethanol solutions (in a 4 l vessel at 20 ± 2 °C), and the mixture was stirred for 10 min and then filtered. The filter residue was dried for 16 h at 40 °C on a tray in an oven and the dried fractions were passed through a 355 μm sieve to remove agglomerated lactose particles. For each sieve fraction two duplicate batches were prepared.

2.3. Mixture preparation and homogeneity testing

Each of the lactose sieve fractions was mixed with 0.4; 1.0; 2.0 or 4.0% (w/w) budesonide in a stainless steel container of 160 cm^3, using a Turbula mixer type T2C (W.A. Bachofen, Basel, Switzerland) at 90 rpm for 10 min. The batch size was 25 g.

Homogeneity was determined on 20 samples per mixture of 25 (±1.0) mg each. The samples were dissolved in 20 ml of ethanol of analytical grade and the UV-adsorption was measured at 243.7 nm, using a UNICAM UV 500 spectrophotometer (ThermoSpectronic, Cambridge, UK). Prior to UV measurement the solutions were clarified by removing non dissolved lactose particles with a centrifuge (Hettich Rotana, Tuttlingen, Germany) during 5 min rotation at 3000 rpm.

2.4. Characterization of the carrier lactose 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 3.0 bar). A lens of 200 mm was used and calculations were based on the Fraunhofer theory. All data given are the mean of three measurements.

The specific surface areas (m^2/g) of the fractions were measured with nitrogen adsorption (9-point BET: TriStar, Micromirectics, UK). The surface roughness index (SRI) has been defined as the ratio between the surface area from nitrogen adsorption to the calculated surface area (CSA), which is based on the median sieve fraction, assuming that the particles are spherical.

The angle of repose has been used to measure the powder flowability.

UV-absorption of 5% aqueous lactose solutions, measured with a UNICAM UV 500 spectrophotometer (ThermoSpectronic, Cambridge, UK) at 280 nm (at room temperature), was used to express the amount of water soluble impurities in the lactose fractions. Because the solutions were clear, filtration was not necessary.

The shape of the carriers was observed under a (Nikon SMZ-U) light microscope. Images of the carrier particles were taken with a (Nikon DN 100 Digital Net) camera and analyzed with Sigma Scan Pro 5 computer software (Jandel Scientific, Erkrath, Germany). More than 250 particles from each of the untreated and treated sieve fractions were photographed and their shape was quantified by the shape factor, the elongation ratio and the surface factor, as defined in equations 1, 2 and 3 (Zeng et al., 2000a), respectively:

$$\text{shape factor}: \quad \mathrm{SHF} = 4\pi A P^{-2} \tag{1}$$

$$\text{elongation ratio}: \quad E = L\mathrm{W}^{-1} \tag{2}$$

$$\text{surface factor}: \quad \mathrm{SUF} = \mathrm{SHF}(1+E)^2\pi^{-1}E^{-1} \tag{3}$$

where A is the projection area of the particle, P its perimeter, L the length of the particle and W the particle width.

2.5. Air jet sieve test

An air jet sieve test (Iida et al., 2003; Flament et al., 2004) was used to assess the rate of drug detachment from the carrier crystals in an air stream. Approximately, 10.0 g of mixture was sieved with a 44 μm sieve using an Air Jet Sieve (Alpine A200, Augsburg, Germany) for 6, 16, 36, 120, 440 and 900 s. The drug concentration was determined using the procedures as described for homogeneity testing for four 25 mg samples taken from the mixture before and after sieving. The detachment rate in Table 3 is expressed with a single parameter, which is the sieving time within which 50% of the drug particles is released (T_{50}). The results given are the mean of four replicate measurements. The experiments were carried out at 20 ± 2 °C and a relative humidity of 50 ± 5%.

2.6. 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, which generates inertial separation forces and retains carrier particles during inhalation. The test inhaler has no dose system: individual doses of 25 mg were weighed and inserted manually. After inhalation, the retained carrier particles were removed from the device and analyzed for residual drug (carrier residue: CR).

The second inhaler used was an ISF inhaler (Salvatore, 1976). Powder de-agglomeration in this inhaler is primarily by turbulent shear (drag and lift forces). For the ISF inhaler individual doses of 25 mg were weighed and filled in gelatine capsules nr. 3 and the in vitro deposition from this inhaler (at 30 l/min) has been measured with a multi stage liquid impinger (MSLI: Apparatus C in the European Pharmacopoeia, 3rd ed.). The first stage deposition during cascade impactor analysis was considered to represent the carrier residue. The experiments were carried out at 20 ± 2 °C and a relative humidity of 50 ± 5%.

3. Results and discussion

3.1. Particle shape and surface texture of lactose

Submersion of the two lactose sieve fractions in different ethanol–water mixtures did not change the typical (tomahawk-like) shape of the lactose particles, as can be concluded from the SEM-micrographs (Fig. 1A–C) and the particle shape characteristics in Table 1. No significant differences can be found in any of the three shape factors. There are considerable differences in the specific surface area (BET) however (Table 2). The significant reduction in specific surface area due to submersion (for both fractions) cannot be explained with a reduction in particle size, as the changes therein (represented by the X_{50}-value from laser diffraction analysis in Table 2) are negligible. Consequently, the surface roughness index decreases proportionally with the specific surface area from nitrogen adsorption. Furthermore, there may be a correlation with the surface impurities, as the E280 decreases substantially too (Table 2). The greatest contribution to a decreased surface area may have been produced by from removing the adhering fines however, as shown in Fig. 2A–C. This is especially the case after submersion in 80% ethanol (Fig. 2C), when practically all fines have been removed from both the carrier surface discontinuities and the smooth crystal planes.

The results in Table 2 show that different degrees of surface smoothing and cleaning can be achieved with a simple submersion technique using different ethanol–water mixtures. The results are in agreement with those presented by Iida et al. (2003) who also did not find changes in the particle size (for Pharmatose 200M) after submersion of the crystals in 70% ethanol, but observed a reduction in the surface roughness too. Also Young et al. (2002) reported a decreasing specific surface area from nitrogen adsorption after particle smoothing as a result of wetting of a lactose sieve fraction with a 5:3 water:ethanol solution in a high-speed mixer under vacuum at 50 °C. In contrast, Zeng et al. (2001a) found a reduction in particle size as well as an increase in the specific surface area. They used similar procedures (rinsing with 96% ethanol), but their submersion experiments lasted considerably longer (over 48 h), whereas they also used a much higher drying temperature (70 °C for 3 h). The likely consequence of this procedure is partial (surface) dehydration of the alpha-lactose monohydrate crystals (Lerk et al., 1983; Lerk, 1987). Because anhydrous alpha-lactose has a higher density than the monohydrate, dehydration introduces small cracks and pores in the surface of the crystals, which increase the specific surface area dramatically. Such small surface asperities have indeed been described by Zeng et al. (2001a), who also reported that the crystals were shiny and polished before submersion and dull after the solvent treatment. Table 2 finally shows that the angle of repose was not changed significantly by the submersion treatment. This seems comprehensible, as the particle size distribution remains the same and the changes in surface irregularities are confined to removal of adhering fines in the micron range.

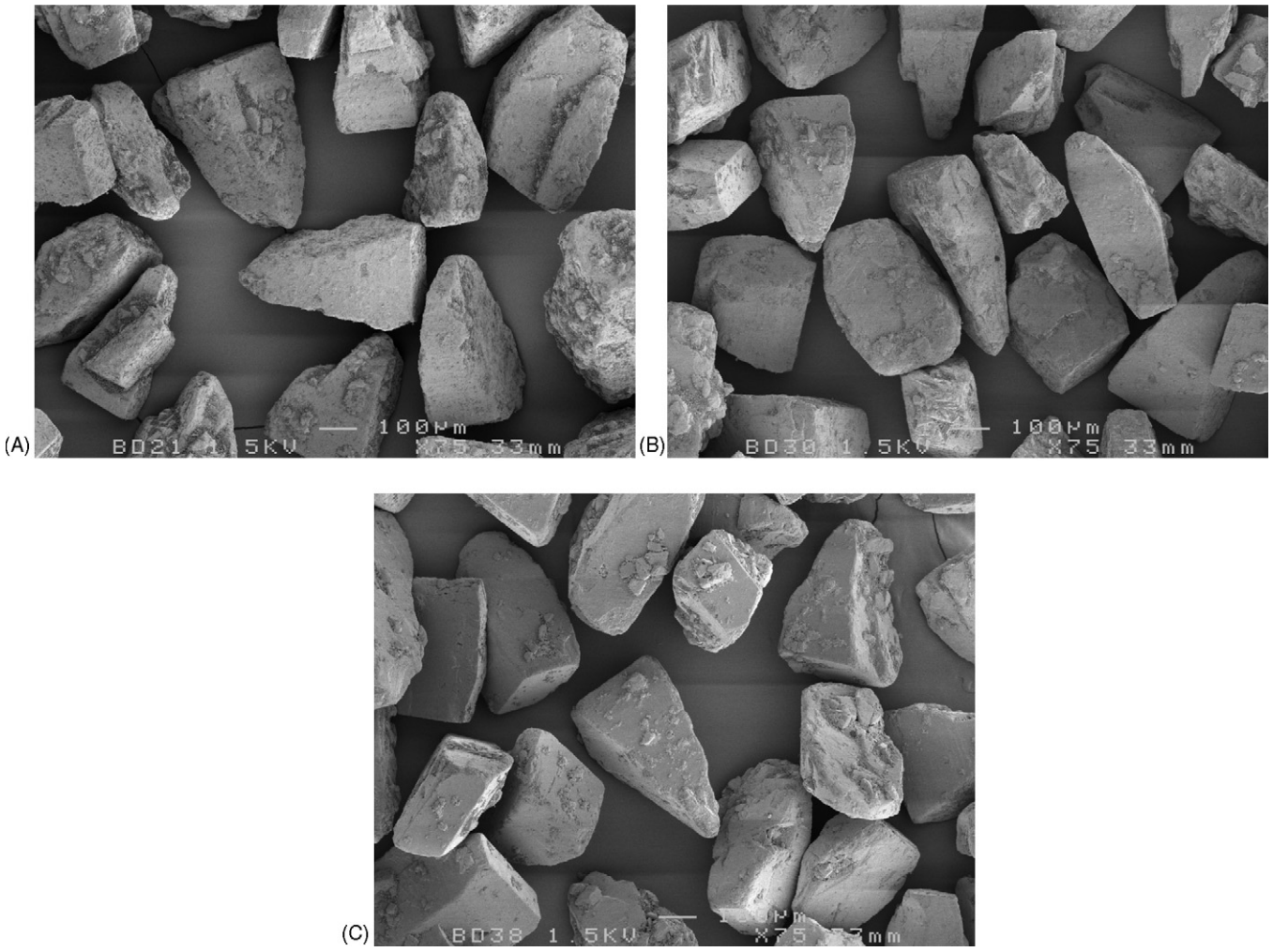

Fig. 1. Scanning electron micrographs showing the particle shape and size distribution of carrier fraction 250–355 μm before (A), and after submersion in 96% ethanol (B) and 80% ethanol (C), respectively. Magnification 75×.

3.2. Results from carrier residue experiments

Fig. 3 shows the carrier residue (CR) obtained with the test inhaler at 30 and 60 l/min as function of the initial carrier surface payload in mg per square meter of carrier surface area. The relationships for the untreated carrier fractions are in good agreement with those from previous experiments (Dickhoff et al., 2003). At 30 l/min, CR decreases with increasing payload for the fraction 63–90 μm due to an increasing excess of drug particles relative to the number of strong bonding places and as a result of the fact that the press-on forces during mixing are relatively low. In contrast, CR for the coarse carrier fraction increases at higher payloads, due to an increasing effectiveness of the relatively high press-on forces. This is for the range of payloads at which (theoretically) a monolayer of drug particles around the carrier is exceeded.

Submersion of the carrier particles increases the carrier residue for both carrier fractions (at 30 l/min). This is explained by the observed removal of adhering fines (Figs. 1 and 2), that may have changed the effectiveness of the press-on forces during mixing. Some of the coarsest adhering fines (5–10 μm) have larger diameters than the largest drug particles. During mixing, they act as a buffer between two colliding carrier crystal planes (Fig. 4), which have been defined as pseudo-active sites previ-

Table 1
Shape factor, elongation ratio and surface factor of untreated and treated lactose sieve fractions as defined in Section 2.4 ($n > 250$)

	Shape factor	Elongation ratio	Surface factor
Untreated (250–355 μm)	0.671 ± 0.071	1.562 ± 0.190	0.895 ± 0.093
Treated with 96% ethanol	0.681 ± 0.080	1.573 ± 0.180	0.908 ± 0.085
Treated with 80% ethanol	0.664 ± 0.073	1.556 ± 0.180	0.895 ± 0.079
Untreated (63–90 μm)	0.662 ± 0.062	1.538 ± 0.198	0.894 ± 0.075
Treated with 96% ethanol	0.666 ± 0.071	1.538 ± 0.231	0.899 ± 0.075
Treated with 80% ethanol	0.670 ± 0.066	1.561 ± 0.251	0.913 ± 0.072

Table 2
X_{50}-value determined by laser diffraction analysis (RODOS dispersion at 3 bar), surface area determined by nitrogen adsorption (BET), calculated surface area (CSA), angle of repose, UV adsorption at 280 nm of a 5% aqueous solution (E280) and surface roughness index (SRI = BET/CSA) for the untreated and treated lactose sieve fractions

	X_{50} (μm) ($n = 3$)	BET (m^2/g)[a]	CSA (m^2/g)	Angle of repose[b]	E280[c]	Surface roughness index
Untreated (250–355 μm)	347.77 ± 1.78	0.0897 ± 0.0057	0.0129	38.21 ± 0.54°	0.030 ± 0.001	6.96
Treated with 96% ethanol	343.95 ± 1.98	0.0682 ± 0.0057	0.0129	37.01 ± 0.36°	0.026 ± 0.001	5.28
Treated with 80% ethanol	341.22 ± 0.51	0.0410 ± 0.0058	0.0129	35.99 ± 0.22°	0.022 ± 0.001	3.18
Untreated (63–90 μm)	93.44 ± 0.12	0.1944 ± 0.0032	0.0509	47.82 ± 0.58°	0.060 ± 0.001	3.73
Treated with 96% ethanol	94.05 ± 0.07	0.1740 ± 0.0047	0.0509	45.40 ± 0.22°	0.040 ± 0.001	3.42
Treated with 80% ethanol	93.51 ± 0.02	0.1194 ± 0.0080	0.0509	49.74 ± 0.88°	0.027 ± 0.002	2.23

[a] Data are presented as mean ± S.D. ($n = 6$).
[b] Data are presented as mean ± S.D. ($n = 5$).
[c] Data are presented as mean ± S.D. ($n = 4$).

ously (Dickhoff et al., submitted). Thus, the adhering lactose fines provide shelter from the press-on forces to smaller drug particles attached to the same crystal planes. The magnitude of the press-on forces increases with the mean carrier diameter. This explains why the effect of submersion is much higher for the fractions 250–355 μm than for the fraction 63–90 μm, particularly at the lower payloads. The increase in adhesive forces for the coarsest carrier fractions at the lower payload could be so extreme in the absence of fine lactose particles (that function as a buffer), that the effect is even noticeable at 60 l/min. At this higher flow rate, at which only particles attached to the strongest bonding sites cannot be removed (Dickhoff et al., submitted), the CR is about the same before and after carrier submersion (at all carrier payloads) for the carrier fraction 63–90 μm. This sug-

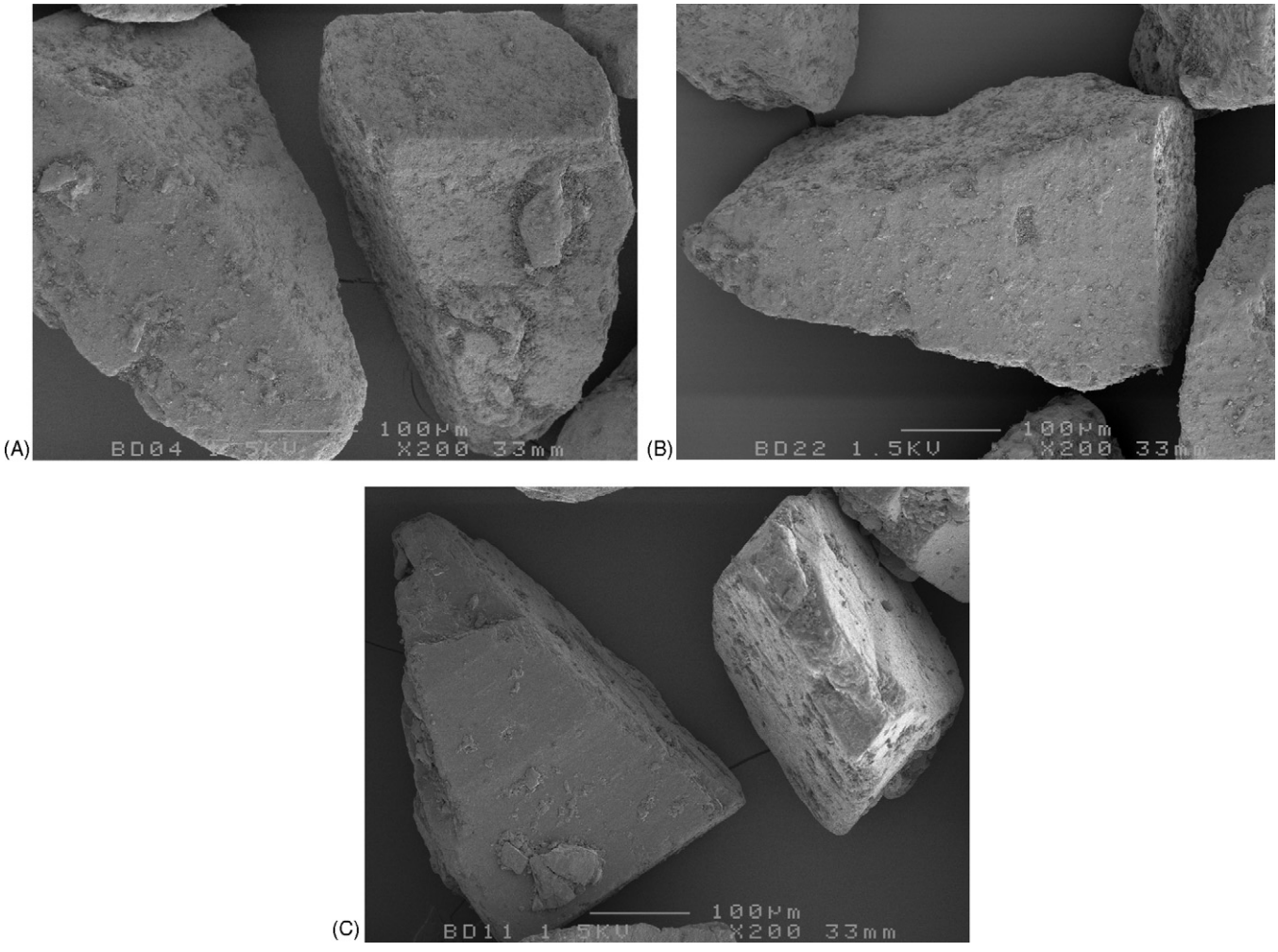

Fig. 2. Scanning electron micrographs showing the surface properties (and amounts of adhering fines) of carrier fraction 250–355 μm before (A), and after submersion in 96% ethanol (B) and 80% ethanol (C), respectively. Magnification 200×.

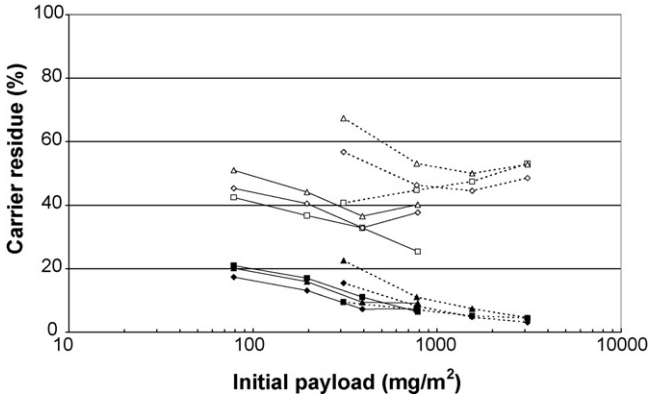

Fig. 3. Carrier residue (%) as function of the initial carrier surface payload (mg/m^2) for two different carrier size fractions. Dotted lines refer to fraction 250–355 μm; continuous lines to fraction 63–90 μm. (■) for untreated fractions; (♦) after submersion in 96% ethanol; (▲) after submersion in 80% ethanol. Open symbols refer to 30 l/min; closed symbols to 60 l/min ($n = 2$).

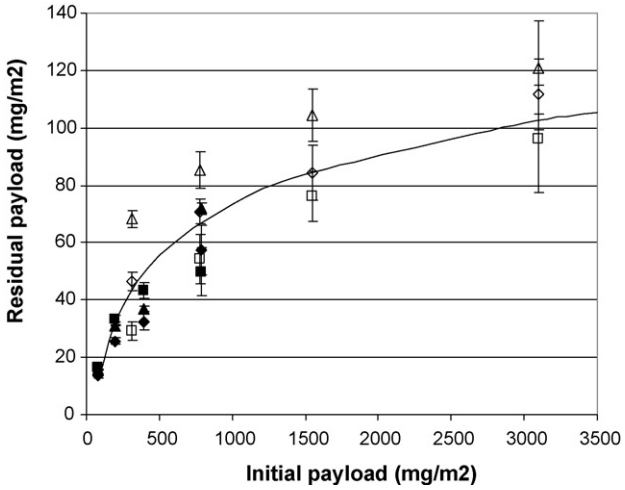

Fig. 5. Residual payload (mg/m^2) as function of the initial surface payload (mg/m^2) for two different carrier fractions measured with the test inhaler at 60 l/min. (■) for untreated fractions; (♦) after submersion in ethanol 96%; (▲) after submersion in ethanol 80%. Open symbols refer to the fraction 250–355 μm; closed symbols to the fraction 63–90 μm.

gests that the potential of the strongest bonding sites has not been changed by submersion, which seems to confirm a previously drawn conclusion that the strongest binding forces between drug and carrier are not primarily related to adhering fines and carrier surface impurities (de Boer et al., 2003).

Previously, it has been calculated that the strongest binding sites for a carrier fraction 250–355 μm become saturated at an initial surface payload of approximately 3000 mg/m^2 (de Boer et al., 2005), depending on the batch of lactose and mixing conditions used. Fig. 5 shows that the surface payload needed to achieve saturation of the active sites for both carrier fractions in this study (from a different batch of lactose) may be somewhat higher as that for the batch used in the previous study, but the saturation concentration has the same order of magnitude (approx. 120 mg/m^2 versus 130–145 mg/m^2 in the previous study). Moreover, there is only a relatively small difference between the saturation concentrations of the untreated and submersed carrier fractions. The ratio of the highest and lowest value in Fig. 5 (at 3100 mg/m^2) is only 1.26. In comparison, the ratio of SRI for untreated crystals to SRI for the submersed crystals (for the coarse fraction) is 2.2 (Table 2). This again suggests that the strongest binding places are not necessarily related to carrier surface rugosity (alone). The E280-value, having a ratio of 1.36 for the untreated to submersed (coarse) crystals (Table 2), has a much better proportionality with the saturation concentration of the active sites (as derived from Fig. 5).

3.3. Results obtained from the air jet sieve test and with the ISF-inhaler

The carrier residue data presented above are the result of the application of inertial separation forces. Previously, it has been proposed that the type of separation forces may influence the drug detachment during inhalation (Dickhoff et al., submitted). To investigate, whether the effect of carrier submersion on drug detachment is the same when drag and lift forces are applied, air jet sieve tests and inhalation experiments with the ISF inhaler were conducted.

Under the standardized conditions for a sieve test as described by (Iida et al., 2003; Flament et al., 2004), the results are not influenced by uncontrolled effects such as incomplete emptying of capsules and blisters. Table 3 shows the T_{50}-values of drug mixtures with both sieve fractions before and after submersion in ethanol–water mixtures obtained with the air jet sieve test for two different carrier payloads. The high values found for the

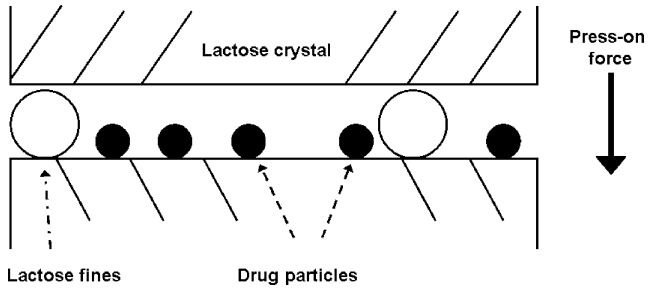

Fig. 4. Schematic drawing of two carrier crystal planes making contact with each other during mixing. The drawing shows how the large adhering fines protect the drug particles against press-on forces.

Table 3
T_{50}-values from the air jet sieve test ($n = 4$)

	T_{50} (s)	T_{50} (s)
	0.4% payload	4.0% payload
Untreated (250–355 μm)	175 ± 12	202 ± 7
Treated with 96% ethanol	205 ± 20	235 ± 18
Treated with 80% ethanol	225 ± 4	255 ± 3
Untreated (63–90 μm)	27 ± 2	20 ± 1
Treated with 96% ethanol	40 ± 1	32 ± 3
Treated with 80% ethanol	93 ± 2	67 ± 2

250–355 μm-fraction confirm that coarse carrier fractions are disadvantageous when drug removal from the carrier particles depends on drag and lift forces (as in turbulent shear inhalers). The differences between the fractions in Table 3 are much larger than in Fig. 3 where approximately 50% detachment is achieved in 3 s inhalation time for both fractions. The differences in time between Table 3 and Fig. 3 to obtain 50% detachment also confirms that inertial separation forces are much more efficient than drag and lift forces. Large carrier particles have large surface discontinuities inside which drug particles are wiped together during mixing (Kulvanich and Stewart, 1987; de Boer et al., 2005) from where they cannot effectively be removed by air current forces. Submersion of the carrier crystals increases the T_{50}-value for both carrier fractions, which is in agreement with the results from carrier residue measurements (Fig. 3).

As with the air jet sieve test, drug particles are detached from the carrier crystals in the ISF-inhaler mainly by drag- and lift-forces. The ISF-inhaler does not retain carrier crystals like the test inhaler however. Therefore, the first stage deposition in the MSLI has been measured to assess the fraction of drug not detached from the carrier crystals during inhalation. Carrier particles within the size fractions 250–355 and 63–90 μm are deposited on this first stage which has a theoretical cut-off diameter for lactose (with a density of 1.54 g/cm^3) of only 24 μm at 30 l/min. As expected, the effect of carrier submersion on drug detachment in the ISF-inhaler (Table 4) is the same as for the air jet sieve. Carrier submersion increases the T_{50}-values from the sieve test for both fractions at both payloads, and the carrier residue for the ISF-inhaler increases also, although to a lesser extent. Both effects indicate that detachment from untreated carriers is easier than from submersed fractions. However, the carrier residues obtained with the ISF-inhaler are lowest for the carrier fraction 250–355 μm (at 0.4% payload), whereas the T_{50} values obtained with the sieve test are shortest for the finest fraction. This discrepancy can be explained with differences in the capsule residues. Capsule residues for the coarse fraction at 0.4% payload (approx. 15%) after inhalation were much higher than those for the fraction 63–90 μm (approx. 7%), indicating that the coarse particles have not been discharged from the capsule completely during inhalation. This confirms that uncontrolled effects may influence the detachment results obtained with marketed inhalers. Uncontrolled effects (e.g., tribocharge) may also have influenced the sieve test results, which could explain why the effect of surface treatment for the fraction 63–90 μm is much higher during the sieve test (Table 3) than during inhalation with the ISF inhaler (Table 4). There are indications for the occurrence of tribocharge, particularly for the rinsed fractions, which have a reduced surface conductivity as a result of the removal of salts and water containing peptides and proteins. Particles were found to adhere to the lid of the sieve.

Table 4
First stage deposition (representing carrier residue: CR) as function of the payload; 30 l/min (3 s) with the ISF inhaler

	CR (%)	CR (%)
	0.4% payload	4.0% payload
Untreated (250–355 μm)	61.92 ± 0.91	72.17 ± 1.21
Treated with 96% ethanol	69.34 ± 0.89	75.31 ± 1.12
Treated with 80% ethanol	73.17 ± 1.12	74.72 ± 1.02
Untreated (63–90 μm)	72.84 ± 0.75	56.86 ± 0.76
Treated with 96% ethanol	75.36 ± 0.36	62.66 ± 0.86
Treated with 80% ethanol	78.30 ± 0.65	64.90 ± 0.91

3.4. Comparative evaluation of carrier submersion results

The results obtained with both inhalers and the sieve test in this study suggest that the way in which drug particle detachment from carrier crystals during inhalation is influenced by carrier submersion in ethanol-water mixtures, is largely independent of the type of detachment forces used. Fig. 6A and B compare all data from this study. In these figures not the T_{50}-values from the air jet sieve test are given (as presented in Table 3), but the percentages detached after 6 s, which are more comparable with the fractions detached by the inhalers within 3 s and less influenced by tribocharge. In all experiments, the percent of drug released from carrier was reduced, or remained at least the same, after carrier treatment. In no case an increase has been obtained.

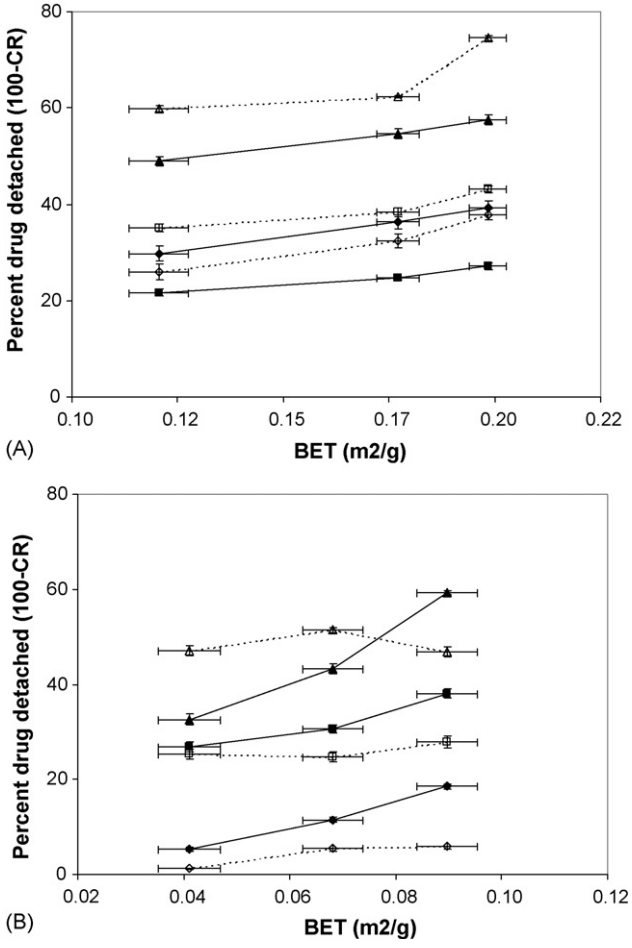

Fig. 6. Percent drug detached from the fraction 63–90 μm (A) and fraction 250–355 μm (B) as function of the specific surface area (BET) in m^2/g (at 30 l/min). Open symbols refer to 0.4% payload; closed symbols refer to 4.0% payload. (■) ISF inhaler (3 s); (♦) air jet sieve test (6 s); (▲) test inhaler (3 s).

Although in Fig. 6A and B the percent of detached drug has been plotted as function of the specific surface area from nitrogen adsorption, no clear unique relationship between both parameters has been obtained. Considering the observed removal of adhering lactose fines from the carrier surface, which may act as a buffer between two colliding carrier particles during mixing, thereby reducing the effectiveness of the press-on forces, this could not be expected. The magnitude and effectiveness of these forces depend on the carrier payload and carrier size fraction. This explains why the decrease in percent drug detached (with increasing carrier surface smoothness) is highest for the mixtures with the coarse carrier fraction at 4% payload (Fig. 6B: closed symbols). For the finer carrier (Fig. 6A) the press-on forces are much lower. With decreasing payload the effectiveness of the press-on forces reduces for both fractions as the drug particles find shelter from these forces in the carrier surface irregularities.

The results in this study are in agreement with those presented by Zeng et al. (2001a) who did not study the carrier residue, but obtained a decreased fine particle fraction (for salbutamol sulphate from the Rotahaler) after carrier submersion. Yet the explanations given are different. Zeng et al. observed an increased carrier surface roughness after solvent treatment, most likely as the result of partial surface dehydration (as explained in paragraph 3.1). Under the milder drying conditions applied in our study, no surface dehydration has been obtained. Our results are in disagreement with those presented by Colombo et al. (2000) and Young et al. (2002) who found a moderate increase in the fine particle fraction (for beclamethasone dipropionate, BDP, from the Pulvinal multi-dose inhaler) after wetting of the carrier with a water:ethanol mixture (5:3). Their procedures were different from ours however, and included the application of high mechanical forces during mixing in a high-speed mixer at 400 rpm. They also used relatively small amounts of wetting liquid. This may not only have caused the observed smoothing of the carrier surfaces, but it could also have increased the amount of adhering lactose fines by wear of the crystals considering that rounding of the crystal edges was reported. Iida et al. (2003) also presented improved in vitro inhalation results after carrier surface treatment with a 70% aqueous ethanol solution. They reported the appearance of microscopic asperities on the carrier surface of a magnitude smaller than the drug particle dimensions after longer wetting times. As explained by Iida et al., such asperities are likely to decrease the contact area between drug and carrier particles and by that, the adhesive force. Because such asperities were not obtained in our study, a reduction of the adhesive force could not be expected. Whether such asperities are obtained or not may not only depend on the drying conditions (referring to partial surface dehydration), but also on the composition of the submersion fluid, stirring conditions during submersion, washing after submersion and type of starting material used. Iida et al. (2003) used a relatively fine (ground) carrier lactose (Pharmatose 200 M), whereas in our study sieved Pharmatose 80 M was used. A ground lactose like Pharmatose 200 M may not only have many local dislocations (where dissolution in a 30:70 water:ethanol mixture is likely to start); it also exhibits poor flow properties as a result of which the press-on forces during mixing are less relevant during mixing.

The differences in results between different studies indicate that the effect of carrier surface treatment on drug detachment from carrier crystals during inhalation depends on the precise conditions and procedures used. They also seem to indicate that the carrier surface characterization techniques used in these studies are not specific and discriminating enough. In our study, no good relationship between the specific surface area (from nitrogen adsorption) and carrier residue was obtained, as the surface area varies with the amount of adhering fines and impurities as well as with the carrier surface irregularities. Besides, there is an effect of the press-on forces during mixing on the drug-to-carrier interaction, of which the relevance varies with the carrier size and payload. In the study of Iida et al. (2003) surface roughness measurements could not reveal the appearance of small asperities in the carrier surface after longer submersion times. But there was a reasonable proportionality between presented surface roughness data and average adhesion force for shorter wetting times. In contrast, Young et al. (2002) measured only a minor decrease in the average separation energy after surface treatment (0.77×), which did not reflect the strongly decreased surface roughness (0.25×). In both studies different techniques for measurement of the adhesive force were used however. Young et al. (2002) used atomic force microscopy with a BDP-probe attached to the cantilever to measure the separation energy for this drug in contact with lactose. In contrast, Iida et al. (2003) used an ultracentrifuge to calculate the average separation force between salbutamol sulphate and lactose carrier particles after 5 min of mixing. Considering the possible effect of the press-on forces during mixing on the adhesive forces between drug and carrier particles, it may be questioned whether atomic force measurements provide the correct information for such studies.

4. Conclusions

The present study suggests that submersion treatment of lactose carrier sieve fractions in ethanol–water mixtures under the conditions described is unfavourable for drug particle detachment from carrier crystals during inhalation. It has been shown that the submersion of carrier lactose neither changes the shape nor the size of the lactose particles. However, the specific surface area by nitrogen absorption may decrease considerably due to the removal of adhering fines and impurities. The first can be observed with scanning electron microscopy; the latter is expressed in a reduction of the absorption (at 280 nm) of a 5% aqueous lactose solution. The removal of adhering lactose fines seems to result in an increased effectiveness of the press-on forces during mixing, which are responsible for increasing the adhesive forces in the mixture. This explains why the effect of submersion in this study was found to depend on the carrier size fraction and the carrier payload. The obtained effect was greatest for the coarsest fraction at the lowest payload, for which the press-on forces are most relevant (as has been shown in previous studies, e.g., Dickhoff et al. (2003). The effect of submersion appeared to be independent of the type of separation force applied however, despite considerable differences in separation effectiveness between the inhalers (and sieve test) used in this study.

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