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Air classifier technology (ACT) in dry powder inhalation Part 2. The effect of lactose carrier surface properties on the drug-to-carrier interaction in adhesive mixtures for inhalation

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Abstract

The effect of carrier surface properties on drug particle detachment from carrier crystals during inhalation with a special test inhaler with basic air classifier has been studied for mixtures containing 0.4% budesonide. Carrier crystals were retained in the classifier during inhalation and subsequently examined for the amount of residual drug (carrier residue: CR). Carrier surface roughness and impurity were varied within the range of their appearance in standard grades of lactose (Pharmatose 80, 100, 110, 150 and 200 M) by making special sieve fractions. It was found that roughness and impurity, both per unit calculated surface area (CSA), tend to increase with increasing mean fraction diameter for the carrier. Drug re-distribution experiments with two different carrier sieve fractions with distinct mean diameters showed that the amount of drug per CSA (drug load) in the state of equilibrium is highest for the coarsest fraction. This seems to confirm that surface carrier irregularities are places where drug particles preferentially accumulate. However, a substantial increase in surface roughness and impurity appears to be necessary to cause only a minor increase in CR at an inspiratory flow rate of 30 l/min through a classifier. At 60 l/min, CR is practically independent of the carrier surface properties. From the difference in CR between 30 and 60 l/min, it has been concluded that particularly the highest adhesive forces (for the largest drug particles) in the mixture are increased when coarser carrier fractions (with higher rugosity) are used. Not only increased surface roughness and impurities may be responsible for an increase in the adhesive forces between drug and carrier particles when coarser carrier fractions are used, but also bulk properties may play a role. With increasing mean carrier diameter, inertial and frictional forces during mixing are increased too, resulting in higher press-on forces with which the drug particles are attached to carrier crystals and to each other.

Keywords: Dry powder inhalation; Air classifier technology; Adhesive mixtures; Carrier surface properties; Lactose; Force Distribution Concept (FDC)

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1. Introduction

1.1. Carriers in adhesive mixtures for inhalation

The choice of type and size fraction of carrier excipient in adhesive mixtures for inhalation is often primarily made to fulfill the basic requirements of homogeneous drug dilution and accurate dose metering. Additionally, the excipient has to be chemically inert in combination with the drug, physically stable and acceptable from toxicological viewpoint. This reduces the freedom of choice for another relevant aspect: the drug-to-carrier interaction forces must be controlled. They have to be strong enough to guarantee good mixture stability during handling, but weak enough to enable the separation forces during inhalation to detach a substantial fraction of the drug dose from the carrier crystals. This requires that the size distributions of the interaction forces (during mixing) and separation forces (during inhalation) are balanced properly (de Boer et al., 2003). The adhesive forces between drug and carrier particles depend on many different variables (Table 1). Many approaches have been presented to influence or control the adhesive forces between the drug and carrier (or between drug) particles (Table 2). They include special techniques for particle engineering of inhalation drugs which are beyond the scope of this paper, however.

Different size fractions of alpha lactose monohydrate have been investigated regarding the powder flow from perforated capsules (Bell et al., 1971), amount and properties of the obtained fine particle fraction (FPF) during inhalation (Steckel and Müller, 1997; Podczeck, 1999), the adhesion force between drug and carrier particles (Podczeck, 1998a), and the site of deposition for the excipient (Pover et al., 1982; Sumby et al., 1993; Silvasti et al., 1996). Although relatively coarse (often rather narrow) carrier fractions are generally recommended as most favorable for the flow properties (Timsina et al., 1994; Hickey and Concessio, 1997), a positive effect on FPF from the presence of fines in the mixture has been recognized. This effect may dominate over carrier particle size and smoothness in determining dispersion and de-agglomeration of drugs during inhalation (Zeng et al., 2001a). Fines may be present in the mixture from attrition (naturally adhering fines), selecting (or blending) lactose grades with wide size distributions (Karhu et al., 2000) or by the addition of certain quantities of fine or intermediate sized lactose to coarser lactose carrier fractions (Arnold et al., 1995; Zeng et al., 1998; Podczeck, 1998a).

1.2. Carrier surface rugosity

The effect of carrier surface rugosity in different degrees of coarseness in adhesive mixtures with relatively high carrier payloads has been investigated by Kawashima et al. (1998). They concluded that microscopically increased surface roughness, as for instance

Table 1
Some parameters that are relevant to drug-to-carrier interaction in adhesive mixtures

	Parameter	Reference(s)
Mixing process	(Degree of) fine particle break-up during mixing	Staniforth (1987), Aulton and Clarke (1996)
	Drug distribution over the carrier particles	Staniforth (1995), Podczeck (1999)
	Type of interaction force between drug and carrier	Hickey et al. (1994), Podczeck (1996), Price et al. (2002)
	The press-on force (between drug and carrier)	Podczeck (1996)
Influenced by	Physico-chemical properties of drug and carrier particles	Most references
	Size and shape distribution of the drug particles	Hickey and Concessio (1997), Podczeck (1998b)
	Conditioning of the starting materials, in respect of:	
	(Equilibrium) moisture content	Podczeck (1997), Maggi et al. (1999), Price et al. (2002)
	Electrostatic behaviour	Staniforth and Rees (1982)
	Carrier size distribution, affecting:	
	Carrier surface conditions	Kawashima et al. (1998)
	Carrier bulk (flow) properties	Unknown
	Carrier payload	Steckel and Müller (1997)
	Mixing conditions, batch size	

Table 2
Approaches to influence or to control the adhesive forces between drug and carrier in adhesive mixtures for inhalation

Method	Reference(s)
By selection of a special carrier size fraction	Steckel and Müller (1997)
By the addition of fines to the carrier	Arnold et al. (1995), Podczeck (1998a)
By selection or control of carrier surface rugosity	Vanderbist and Maes (1998)
By passivation of active carrier bonding sites	Staniforth (1995)
By controlling the adhesive forces, e.g. by means of:	
Engineering of drug particles with super critical fluid technology	Beach et al. (1999)
Engineering of drug particles by (co-)spray-drying with excipients	Venthoye et al. (2001)
Engineering of drug and excipient particles by emulsification techniques and freeze–drying	Edwards et al. (1997, 1998)
Addition of force control agents (FCAs)	Meakin et al. (1998), Begat et al. (2001)

obtained from crystallisation of spray-dried lactose, is most desirable to improve the inhalation efficiency of the Spinhaler. Several other studies in the past 15 years have confirmed that the carrier surface rugosity on a microscale is relevant to the drug-to-carrier interaction in adhesive mixtures for different types of dry powder inhalers (e.g. Ganderton and Kassem, 1991; Staniforth, 1996; Podczeck, 1998b, 1999; Zeng et al., 2000, 2001a). Carrier rugosity as well as sites with higher bonding energy have been described in many different ways (Table 3). They include small discontinuities of crystal planes, such as clefts, grooves and adhering fines resulting from milling and attrition processes. The size of such carrier discontinuities is generally of the same order of magnitude as that of the drug particles. Staniforth (1995) proposed mild treatment in a ball mill as a suitable means to dislodge naturally adhering fines from the surface of coarse carrier crystals and to reattach them to areas of high energy (clefts and grooves), so as to passivate these active sites before drug is mixed with the carrier (preconditioning of the carrier). This so-called corrasion process (although in a different manner) has also been applied by Podczeck (1998a, 1999) who concluded that its effect is only meaningful above certain threshold values for the initial surface roughness. Granular structures, which may also be the result of crystallisation processes (e.g. by coalescence during crystal growth) exhibit pores that are generally large enough to contain relatively large drug agglomerates. Such structures can for instance be found in roller-dried beta lactose (Vanderbist and Maes, 1998) or spray-dried lactose (Harjunen et al., 2002). Different techniques have been proposed to quantify surface rugosity, including laser profilometry (Podczeck, 1999) and air permeametry (Ganderton and Kassem, 1991; Zeng et al., 2001a).

Table 3
Review of terms for carrier surface conditions

Term	Reference(s)
Surface rugosity in terms of:	
Surface asperities and clefts (microrugosity)	Staniforth (1996)
Granular (coalescent) structures (macrorugosity)	Kawashima et al. (1998)
Active sites in terms of:	
Fines	Podczeck (1998a)
Surface rugosity	Ganderton and Kassem (1991)
Surface irregularities (asperities, clefts, fines)	Staniforth (1995, 1996)
Amorphous spots and disorders in crystallinity	Buckton (1997)
Impurities	Price et al. (2002)
Water of adsorption	Price et al. (2002)
A combination of previous parameters	de Boer et al. (2003)

1.3. Carrier polymorphism and degree of impurity

Ahmed et al. (1996), Buckton (1997), Shekunov and York (2000) and many others emphasized the relevance of surface energetics to the interfacial contact between drug and carrier. Partially amorphous or unstable polymophic forms (as from comminution or spray-drying techniques) and changes therein (Harjunen et al., 2002) make the interparticulate contact quite unpredictable and the powder formulation rather unstable. In contrast, relatively little attention has been given to the possible influence of carrier impurities, like salts, urea, water soluble protein residues and peptides, which are the remains of adhering mother liquor and are mainly concentrated on the outside of the carrier particles. They have a different chemical structure, which is relevant to the type and size of the adhesive force (e.g. by a different Hamaker constant). Peptides and protein residues (by their water affinity) largely determine the amount of adsorbed water of crystalline alpha-lactose monohydrate, which is concentrated in the pollution regions in an amount up to 30%, depending on the equilibrium relative humidity (ERH). Also the possible presence of amorphous lactose and different salts can play a role in the water adsorption on the crystal surface. This phenomenon of water concentration in small areas has been termed as amplification of the effect of water (Ahlneck and Zografi, 1990). The presence of surface pollutions and high concentrations of adsorbed water may give rise to the formation of decomposition products, such as hydroxy methyl furfural (HMF), an intermediate product of the Maillard reaction. Only recently, some special techniques have been introduced to produce high purity carrier lactose with high crystallinity and smooth surface, such as crystallisation from Carbogel (Zeng et al., 2001b).

1.4. Neglected aspects and aim of the study

All previously mentioned variables in the interaction between drug and carrier particles result in a wide size distribution for the adhesive forces (de Boer et al., 2003). Although the effects of most of these variables have been investigated separately (Fig. 1), possible interactions between these variables have hardly been studied. Moreover, the influence of the type and size of the removal forces on the FPF from a DPI is often

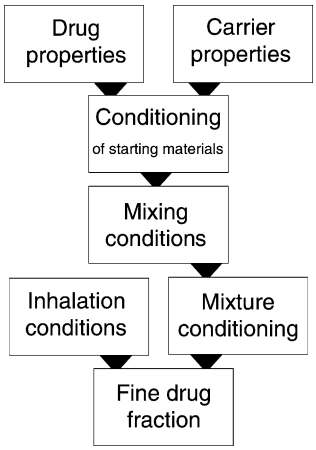


Fig. 1. Schematic, simplified presentation of the variables that influence the fine particle generation from adhesive mixtures during inhalation.

underestimated or simply ignored. In different studies, different dry powder inhalers have been used with different powder de-agglomeration principles. They exhibit different efficiencies in fine particle generation (from adhesive mixtures) and their response to a change in powder properties may be completely different too. Finally, no studies are known to us in which the effect of the carrier bulk properties on the formation of the drug-to-carrier interactions during mixing of inhalation formulations has been investigated systematically. The bulk properties, in combination with the type of mixer, mixing container, filling degree and batch size (influenced by carrier payload) determine the size of the shear, impact and friction (press-on) forces that are relevant to all steps in the mixing process. Changing the mixing conditions or bulk properties may have great effect on drug distribution over and adhesion to the carrier crystals, as shown for example by Podczeck (1996). She investigated the effect of the press-on force with which drug particles were attached to a carrier substrate on the adhesion force between the two and found that an increase in press-on force by a factor 2–3 may increase the adhesion force by a factor 1.5 to nearly 10, depending upon the type of adhering particles and carrier substrate.

Our aim is to optimize the balance between adhesion and removal forces in respect of mixture homogeneity and stability on the one hand, and fine particle resuspension during inhalation on the other,

using air classifier technology. For that, the relevance of carrier surface and bulk properties to the interaction between drug and carrier particles in adhesive mixtures has to be known, in relation to the separation performance of a classifier on these mixtures. In this part of the study, the effect of carrier surface rugosity and degree of impurity of standard alpha-lactose monohydrate (Pharmatose) grades on carrier interaction with budesonide is investigated. In the next part, the effect of carrier bulk properties on drug detachment and detachment rate from the carrier in a basic air classifier will be studied, as well as the influence of the mixing time on that. This provides the necessary information for design and optimisation of an air classsifier family for a marketed dry powder inhaler, which will be reported in the final parts of this series. Results will be explained using a previously described Force Distribution Concept (FDC) (de Boer et al., 2003).

2. Materials and methods

2.1. Materials and special carrier size fractions

Budesonide was supplied as a free sample by Sofotec (Germany) in a size distribution 10% <0.54 μm and 100% <4.60 μm (X_{50} = 1.04 μm) from dry laser diffraction analysis. The budesonide was screened through a 90 μm sieve to break-up (and remove) hard agglomerates before mixing of the drug with the carrier fractions. Narrow carrier size fractions were derived from different grades of lactose (Pharmatose, DMV International, The Netherlands). All size fractions had a relative width (ratio of the span of the size range to the mean fraction diameter) between 0.25 and 0.35. The fractions were prepared in small batches of approximately 100 g by subsequent 20 min vibratory sieving (Analysette 3, Fritsch, Germany) and 20 min air jet sieving (A200, Alpine, Germany).

2.2. Carrier characterisation

Particle size analysis: size distributions of all carrier fractions and quantities of adhering fine lactose particles within these fractions have been measured with laser diffraction analysis (Sympatec HELOS/BF-MAGIC) using a 100 mm lens and the Fraunhofer theory. The fractions were dispersed in the laser beam with a RODOS at 3–5 bar (Sympatec GmbH, Germany).

Scanning electron microscopy was carried out using a JEOL JSM 6301-F microscope (JEOL, Japan). Powder samples were sprinkled on double-sided sticky tape on metal disks and subsequently coated with 150 nm of gold/palladium in a Balzers 120 B sputtering device (Balzers UNION, Liechtenstein).

Specific carrier surface area (S_g; m^2/g) from nitrogen adsorption (BET-method) was obtained with a Quantasorb model QS-14 (Quantachrome Instruments, USA). Samples of approximately 1 g were inserted in test tubes and dried overnight in an oven at 50 °C under helium atmosphere prior to measurement. The desiccated gas mixture (80:20 for nitrogen:helium) was stabilised before measurements were undertaken and the Quantasorb was calibrated between each series of three experiments with the injection of a known volume of the same gas mixture. For each sample, two test tubes were prepared and with each test tube three replicate measurements were performed. All results were corrected for thermo-diffusion peaks.

UV-absorptions of 5% aqueous lactose solutions were measured with a Philips PU 8720 UV-VIS spectrophotometer (Philips, The Netherlands) at 280 nm (at room temperature). Because the solutions were clear, filtration was not necessary.

Moisture sorption and desorption isotherms at 25 °C of Pharmatose 110 M fractions between 0 and 90% relative humidity (%RH) were obtained with a Dynamic Vapour Sorption apparatus, type DVS-1000 (SMS, UK). Relatively large samples of 100 mg were weighed into the sample cup and dried at 0% RH until the rate of change in weight reached a value smaller than 0.0005% per minute. Next, the relative humidity was increased in steps of 10%, but not before the previously mentioned rate of change in weight from the previous step was achieved. The total percent of water uptake (%H_2O) for each carrier fraction between 0 and 90% RH was calculated.

Expression of the results: specific surface area from nitrogen adsorption (referred to as BET), the extinction at 280 nm of a 5% aqueous lactose solution (E-280) and the weight increase between 0 and 90% RH by water sorption (%H_2O) have been expressed per unit calculated surface area (CSA) for each

carrier fraction. Calculation of CSA was based on mean fraction diameters, assuming that the carrier particles are spherical, which includes the introduction of small errors, because the shape of the size distribution of the fractions (volume distribution as function of diameter) is not always symmetrical and sieved α-lactose monohydrate particles are more or less wedge shaped. Since this study is performed with solid lactose crystals, it is assumed that the BET-surface area represents the additional surface area from surface discontinuities (primarily consisting of adhering fines and impurities) only, and that there is no contribution from internal pores. This assumption has been checked with carefully rinsed crystals, for which the ratio of BET to CSA reached a value of 1.00–1.05 (CSA corrected for particle shape). The ratio of BET to CSA has been termed as surface roughness index (SRI).

2.3. Adhesive mixture preparation and characterization

Adhesive mixtures with 0.4% budesonide and different lactose carrier size fractions were prepared in a batch size of 25 g, using a stainless steel mixing container (160 ml) in a Turbula T2C (Willy A. Bachofen AG, Switzerland) tumbling mixer at 90 rpm. Mixing time was 10 min. Mixture homogeneity was tested by taking 20 random samples of 25 mg from each mixture. The samples were dissolved in 15–20 ml of 100% ethanol and the drug solutions were cleared from lactose crystals using a centrifuge (5 min at 3000 rpm; Rotana 3500, Hettich, Germany) and diluted (if necessary) before measuring the drug concentrations spectrophotometrically at 242.8 nm (PU 8720 UV-VIS spectrophotometer, Philips).

2.4. Budesonide re-distribution between dissimilar carrier fractions

Carrier fractions (45–63; 63–90; 90–125; 125–180 and 180–250 μm, respectively) were derived from Pharmatose 100 M according to the procedures in Section 2.1. Small amounts (25 g) of these fractions (having different specific surface areas: CSAs) were blended with different amounts of budesonide to obtain mixtures with the same drug load of approximately 0.12 g/m^2 for all fractions. Mixing procedures were the same as described in Section 2.3. Next, two different mixtures (based on different carrier fractions) were mixed together for a period of 10 min in a weight ratio of 1:1, starting with the finest (45–63 μm) and coarsest (180–250 μm) carrier fractions. Immediately afterwards, the mixtures (carrier fractions) were separated again by mild hand sieving over a 150 μm (or 180 μm) sieve and (25 mg) samples were taken to measure the new drug loads in the original carrier fractions, using the same procedures as described for homogeneity testing (Section 2.3). Mixing, separation procedures and subsequent drug load measurements were then repeated for the same carrier fractions for additional mixing periods of 20, 30 and 60 min, respectively (up to a total mixing time of 120 min for the experiment). The same procedures were applied to the carrier fractions, 63–90; 90–125 and 125–180 μm, all in combination with the coarsest fraction of 180–250 μm, thereby reducing the ratio of coarse to fine for the mean carrier diameters in subsequent experiments. All drug loads were expressed in gram per CSA.

2.5. Carrier residue (CR) measurements

The special test inhaler (CII) with basic air classifier used for the CR experiments has been described previously (de Boer et al., 2003). The test inhaler was connected to a glass constructed four stage impactor of the Fisons type (Elgebe, The Netherlands) so as to use it exactly under the same circumstances as during standard cascade impactor analysis. The impactor was operated in combination with a dry bent induction port for the aerosol with a large radius and a timer controlled solenoid valve to start and stop the flow through the test inhaler. FPFs were actually measured (as a control value) but are not presented in this manuscript as they do not contribute to the discussions. After each inhalation, the retained carrier was removed from the test inhaler and treated similarly to the mixture samples taken for homogeneity testing. The CR values presented are the mean of two series of 10 inhalations of 25 mg of mixture each. CR values have been expressed as percentage of the real dose; all CR values have also been corrected for carrier passage (by linear extrapolation to 100% retention).

3. Results and discussion

3.1. Budesonide re-distribution between dissimilar carrier fractions

Fig. 2 shows the results of the budesonide re-distribution experiments. When two carrier fractions from the same batch of lactose with initially the same drug load (in gram drug per unit CSA) are mixed together for a certain period and subsequently separated, it appears that some drug has migrated from the fine towards the coarse carrier particles. When this process of subsequent mixing together and separating is repeated over longer mixing times, the drug distribution over the surface of both fractions seems to reach an equilibrium (which is established already after 30 min mixing time). The ratio of drug load for the coarse fraction to that of the fine fraction in the state of equilibrium (for the mean values between 30 and 120 min) appears to correlate more or less in a linear way with the mean diameter ratio of the carrier fractions used (for fractions derived from the same batch of lactose). It has been checked that the distribution in the state of equilibrium between two carrier fractions is independent of the initial load of both fractions (results not shown).

Drug re-distribution experiments were undertaken because of some confusing previous work. Podczeck (1998a) showed that the force of adhesion between drug and carrier particles (measured with a centrifuge test) decreases with increasing mean Feret diameter for the carrier fraction. Yet, in a different study, she reported that during inhalation with a Diskhaler (using the same mixtures) slightly less drug is detached from the carrier when only large or medium sized carrier particles are present in the mixture, i.e. when the Feret diameter is relatively large (1999). In the same study (1999), mass median aerodynamic diameters (MMADs) for the fine drug fractions in an Anderson impactor from these mixtures were considerably larger than the MMAD of the primary drug particles. She therefore concluded, that the drug is preferentially adhered to the fine lactose monohydrate particles instead of the coarse ones, forming strong multiple-particle agglomerates that are resuspended during inhalation and deposited in the impactor together. She found support for this explanation by separating the mixtures into two fractions over a 74 μm sieve and analyzing the drug amount in both fractions, coarse and fine, which appeared to be two times higher in the fine fraction for mixtures containing 10 and 20% fines and even three times higher for mixtures with 30% fines.

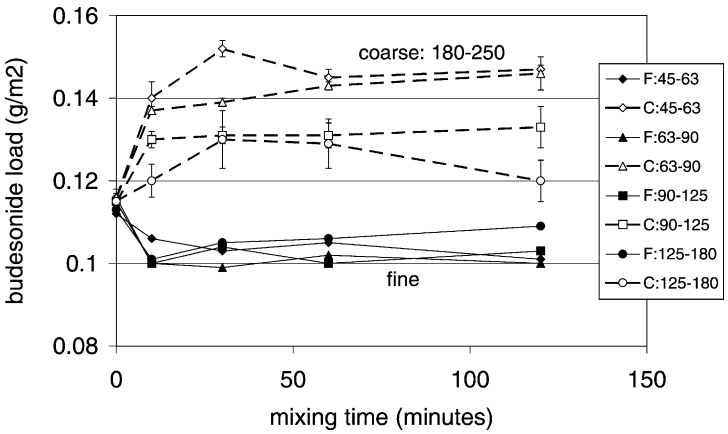


Fig. 2. Budesonide re-distribution between two carrier fractions with dissimilar size distribution from the same batch of Pharmatose 100 M. The graphs show the drug load of each fraction as function of the time during which two different fractions (with initially the same drug load) were mixed together. In all experiments, the coarse fraction was 180–250 μm. Unbroken lines (closed symbols) represent the different fine fractions from different mixing experiments; broken lines (open symbols) are for the matching coarse fraction (180–250 μm) in the experiments. Two matching fractions are indicated with the same symbols, (e.g. C:45–63 refers to the coarse fraction 180–250 μm in the mixing experiment with fine fraction 45–63 μm (referred to as F:45–63). Each data point (drug load) is the mean of 10 samples (25 mg); bars (for the coarse fraction only) indicate S.D. in drug load.

Although this may not seem so, the results in Fig. 2 are in good agreement with those presented by Podczeck (1999), after correction of her values for the difference in specific surface areas between both fractions. From the known density of α-lactose monohydrate (1.54 g/cm^3), the given mean Feret diameters for the different windsifter fractions from each of the lactose grades used in Podczeck's study and the composition of the mixtures (10, 20 and 30% fine lactose), the total surface areas (potential bonding areas for the drug) of the carrier fractions in each of the mixtures can be estimated. For the mixtures with coarse (>70 μm) and fine particles (<20 μm), the ratio of total surface area for the fine fraction to that of the coarse one (on average for all grades of lactose) is approximately 73:27 for the mixtures with 10% fines and 91:9 for the 30% mixtures. Podczeck (1999) found two thirds of the drug in the fine fraction after classification of the mixtures with 10 and 20% fines and three quarters (in the fines) for the mixtures with 30% fines. Drug ratios (fine to coarse) of 2:1 and 3:1 for approximate surface area ratios of 3:1 and 10:1, respectively, must lead to the conclusion that the drug load (g/m^2) was highest in the coarse fractions. Both in our and Podczeck's experiments, it must be assumed that the difference in load between de fractions (fine and coarse) is caused by a difference in carrier surface properties, and not so much by different bulk properties (as for instance expressed in a press-on force), because both fractions were mixed together. Consequently, the bulk properties in the mixture of both fractions were the same for these fractions. A large difference in carrier surface properties for fractions from the same batch of lactose is not expected, however, considering the moderate difference in drug load by a factor of 1.5–2 (Fig. 2).

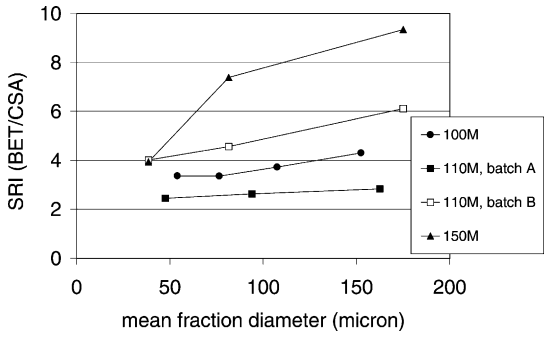


Fig. 3. Surface roughness index (ratio of BET to calculated surface area: CSA) as function of the mean diameter for fractions derived from various batches of Pharmatose. The lines connect size fractions derived from the same batch. The BET-values used for the calculation of SRI are the mean of six replicate measurements.

3.2. Carrier surface roughness index (SRI)

Fig. 3 shows that the ratio of carrier surface area from nitrogen adsorption to CSA, which is the SRI, increases with increasing mean fraction diameter for the lactose batches in the study. This could explain the higher equilibrium drug load on the surface of coarser carrier particles from the re-distribution experiments

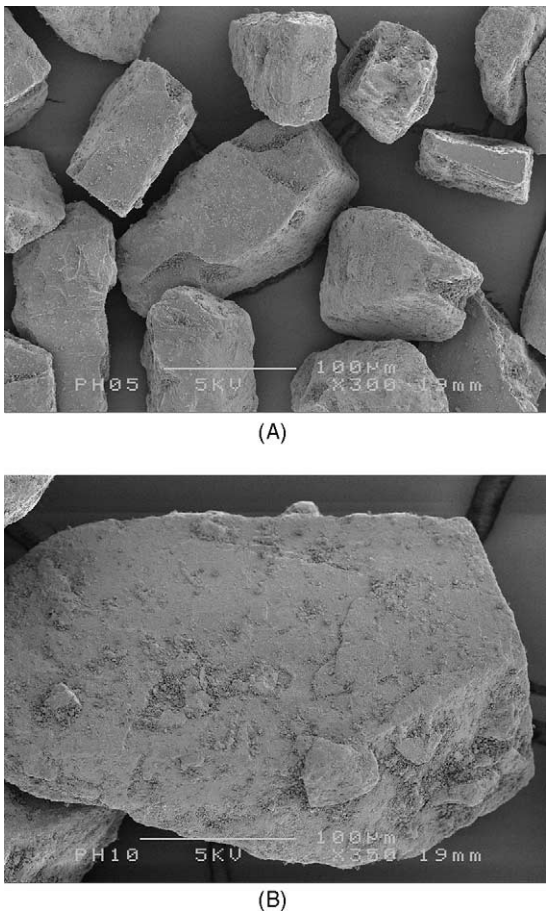


Fig. 4. Scanning electron micrographs of two different carrier sieve fractions derived from Pharmatose 150 M. (A) Fraction 63–100 μm and (B) fraction 150–200 μm. Photographic magnifications are 300× (A) and 350× (B).

(Fig. 2). It is important to realize that although most batches of lactose show the same trend in this respect, occasionally an exception can be found. A higher SRI means more potential for multiple contact points between drug and carrier particles. Surface irregularities on larger crystals are also sites where surface impurities preferentially accumulate, since these are the places where most mother liquor remains when the crystals leave the centrifuge. Impurities like peptides and small proteins may constitute ductile layers (with high water contents) onto which increased contact areas between the drug and carrier particles (and capillary forces) are possible. Fig. 4 shows that for the two different sieve fractions of Pharmatose 150 M, none of the crystals has completely smooth crystal planes. Local projections and depressions exist, against or inside which the naturally adhering fines tend to assemble. Fine drug particles, generally having the same approximate size distribution as these lactose fines, may show the same tendency. This gathering of fine particles (lactose or drug) is not necessarily a consequence of a higher local bonding energy, however. The relatively steep faces of plateaus on the crystal surface, and rifts and valleys in the crystal planes offer shelter to adhering fine particles from shear and friction forces during mixing. Once wiped together in such places by these forces, they may predominantly stay there during the whole mixing process, although a certain re-distribution from these irregularities is not excluded. This depends on the carrier payload and the relative importance of other forces, such as the inertial forces generated during mixing as well as the adhesive forces for drug particles attached to smooth crystal planes. The size of these forces depends at least partially on the bulk properties of the powder, as has been discussed in the introduction. Good flow properties may increase the relevance of inertial forces (e.g. in tumbling mixers).

3.3. Carrier surface impurities

Fig. 5 shows that also the amount of impurities (per unit CSA) increases with increasing mean fraction diameter for the batches in this study. Extinction at 280 nm of a lactose solution is primarily the result of the presence of aromatic amino acids and HMF, which are representative for the water soluble peptides and proteins from the mother liquor. E-280 per CSA shows the same general trend as SRI, because the amount of mother liquor that surrounds the lactose crystals after they leave the centrifuge, increases with increasing carrier surface roughness. There is also a contribution from minor quantities of urea and riboflavin to E-280. Considering the large amount of water (>30%) that peptides and proteins are able to adsorb, compared to alpha-lactose monohydrate, it may not be surprising that the percent weight increase per unit carrier surface area (%H_2O/CSA, Fig. 6) for Pharmatose 110 M

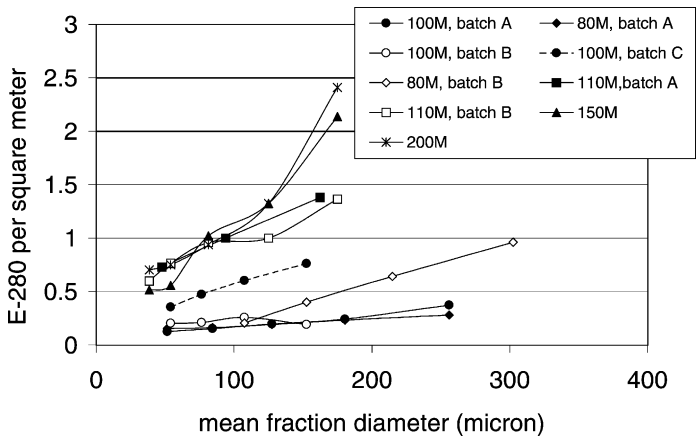


Fig. 5. UV-light extinction at 280 nm (E280) per CSA of 5% aqueous lactose solutions as function of the mean diameter for fractions derived from various batches of Pharmatose. The lines connect size fractions derived from the same batch. Each value is the mean of two duplicate measurements performed on two different solutions prepared from the same sample.

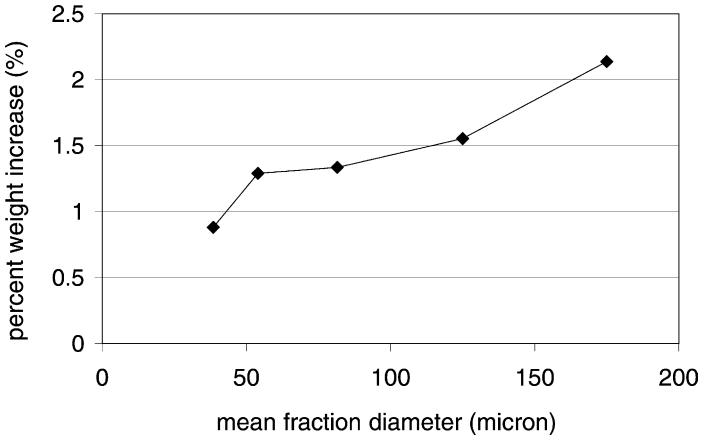


Fig. 6. Percent weight increase (%H_2O) as the result of water uptake between 0 and 90% RH (25 °C) per unit calculated carrier surface area (CSA) as function of the mean diameter for fractions derived from Pharmatose 110 M. Each value is the mean from two different moisture isotherms (for two different samples taken from the same fraction).

(batch B) shows the same trend as function of mean fraction diameter as E-280/CSA (Fig. 5). The relative increases in E-280 and %H_2O (both per CSA) with increasing mean diameter for different size fractions of the same type and batch of lactose appear to match even quite well (Fig. 7), in spite of the fact that the extinction at 280 nm is a very rough, incomplete and non-specific parameter. The relative increase in SRI for the same batch of lactose is slightly lower but confirms the proportionality with both other carrier surface parameters. It is highly unlikely that amorphous lactose fractions play a role in respect of drug-to-carrier interaction, because amorphous lactose already crystallizes after moisture sorption at relative humidities between 45 and 50% (Vromans, 1987; Buckton and Darcy, 1996).

3.4. Carrier residue (CR) measurements

Fig. 8 presents the percent CR as a function of the carrier size fraction for a number of different lactose types. No clear trend can be observed; only fractions derived from two specific batches of Pharmatose 100 and 110 M show an increase in CR with increasing

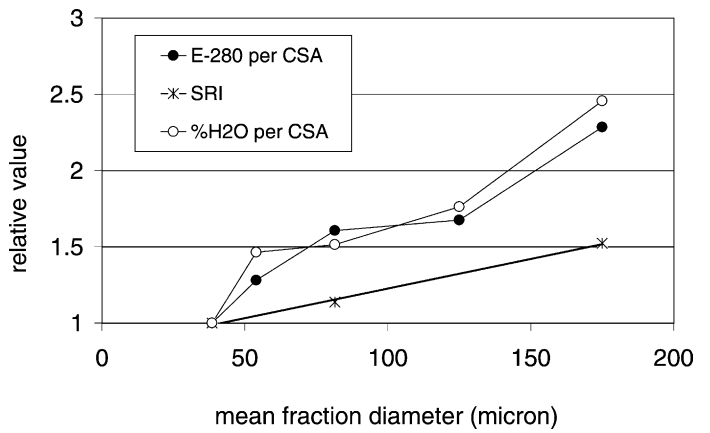


Fig. 7. Relative value of SRI, E-280/CSA and %H_2O/CSA for different carrier size fractions from the same batch of Pharmatose 110 M; the values for the finest fraction (32–45 μm) are the reference values. Data are derived from Figs. 3, 5 and 6.

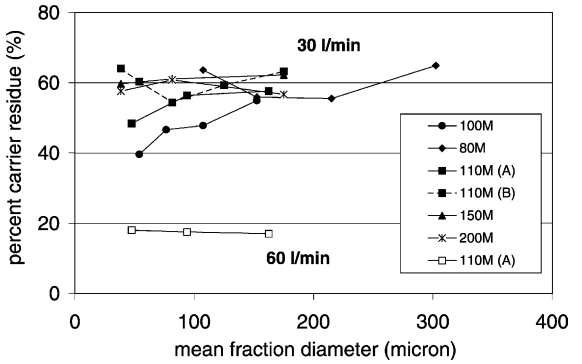


Fig. 8. Carrier residue (CR) as function of mean carrier diameter for carrier fractions derived from different types of Pharmatose for mixtures with 0.4% budesonide. Test inhaler CII; mixing time 10 min; inhalation time 3 s. Each value is the mean of two series of 10 inhalations.

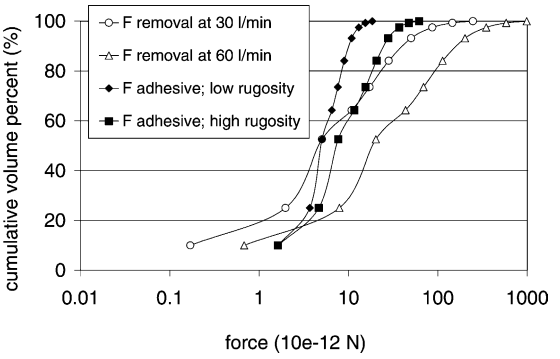


Fig. 9. Force Distribution Concept: schematic presentation of the size distributions for the adhesive forces in the mixture and the removal forces during inhalation with an air classifier (at two different flow rates). Explanation is in the text.

mean fraction diameter (at 30 l/min), as one might be prone to expect from the increasing surface irregularities and impurities. It should be realized that the results from inhalation do not solely reflect the effectiveness of the adhesion forces, however, but also that of the removal forces generated in the inhaler.

The observed effect of carrier surface properties on CR at 30 l/min is much higher than that at 60 l/min, as shown in Fig. 8 for Pharmatose 110 M. High flow rates through an air classifier seem to make this type of de-agglomeration principle less sensitive to variations in the properties of the inhalation powder, which is the reason why most of the experiments were conducted only at 30 l/min. This may have two different reasons, as can be explained with a previously introduced FDC, shown in Fig. 9 (de Boer et al., 2003). The first explanation is that the size distribution curve for the generated removal forces shifts to higher values at higher flow rates through the classifier. As a result, more adhesive forces between the drug and carrier particles can be exceeded and the *Y*-coordinate for the intersection between the size distribution curves for adhesive and removal forces shifts to a lower value (lower CR). This range of *Y*-coordinates corresponds with a part of the distribution curve for the separation forces where the slope is least steep (representing the smallest drug particles in the mixture). So, a shift of the whole distribution curve for the separation forces to higher values has least effect on the *Y*-coordinate for the intersection between both curves within this range of coordinates (range of CR values). The example in Fig. 9 is fictitious, but the size distribution curves for the forces have a realistic shape, based on the S-shaped cumulative volume percent curve for the drug from laser diffraction analysis.

A second explanation is that the highest adhesive forces in the mixture, mainly applied to the largest drug particles, increase more strongly with increasing mean carrier diameter than the lowest adhesive forces by which primarily the smallest drug particles are attached. This also could have two reasons (Fig. 10). Increasing the mean carrier diameter generally results not only in a higher degree of surface rugosity and increased amount of impurities (Figs. 3 and 5), but also in improved flow properties (higher press-on forces

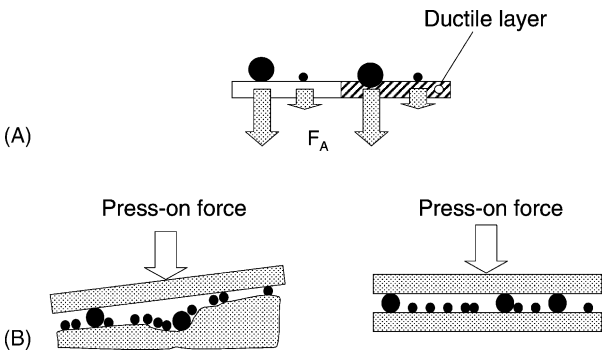
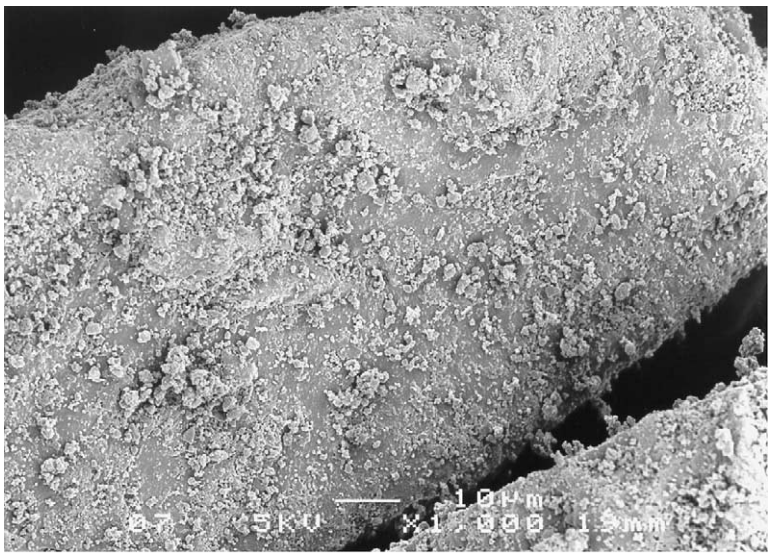
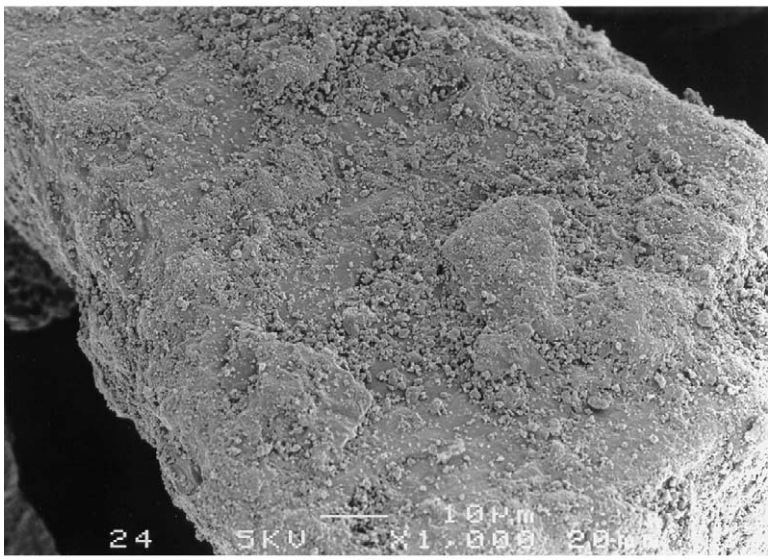


Fig. 10. Possible explanations for the highest increase of predominantly the highest adhesive forces in an adhesive mixture, due to increased press-on forces during mixing and increased carrier surface irregularities (and impurities).

during mixing). The largest drug particles, attached by the highest adhesive forces, suffer from the highest increase in contact area when they are sited onto ductile layers of impurities (Fig. 10A). Because of their large size relative to the size of carrier surface pores, they also have a greater chance of being attached with multiple contact points than small particles. Secondly, larger particles provide shelter to smaller particles from the press-on forces during mixing that are the result of carrier particle collisions (Fig. 10B). Fig. 11A (scanning electron micrograph before inhalation) shows that drug particles occupy both sites with



(A)



(B)

Fig. 11. Scanning electron micrographs of carrier crystals from a mixture with carrier sieve fraction 63–106 μm (Pharmatose 100 M) and 0.68% budesonide before (A) and after (B) inhalation at 30 l/min (3 s) with test inhaler CII.

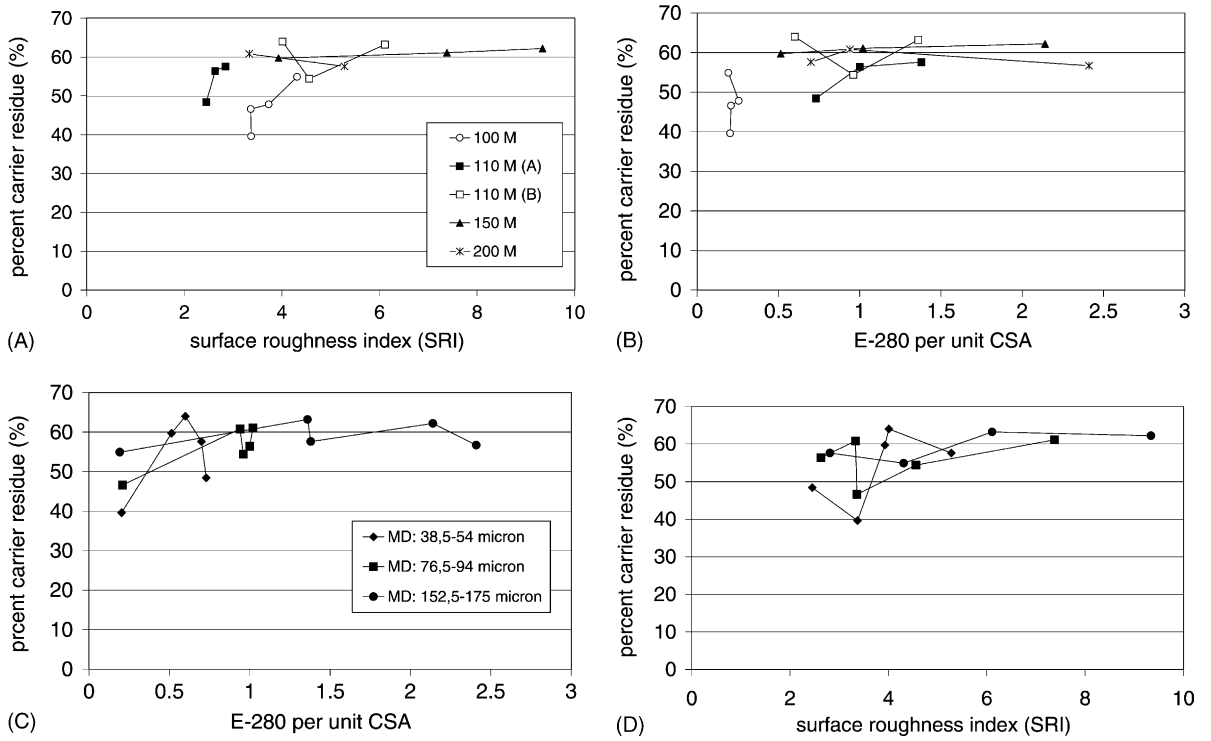


Fig. 12. (A and B) Correlations between CR and SRI (A), respectively between CR and E-280/CSA (B). Linkage is for carrier size fractions derived from the same batch of Pharmatose. (C and D) Correlations as shown in (12A and B; linkage is now for carrier size fractions with approximately the same mean diameter (MD).

irregularities and more or less smooth crystal planes between these irregularities. Fig. 11B shows roughly the same distribution of drug particles over the carrier crystals after inhalation at 30 l/min (for carrier particles retained by the classifier in the test inhaler), proving that detachment is from all binding sites and not solely from the smooth crystal planes. This may explain why the ratio of highest (64.9) to lowest (39.6) value for CR (at 30 l/min) is only 1.6, whereas the same ratio for SRI is 3.8 and that for E-280/CSA is even 19.1.

3.5. Correlations between CR and carrier surface properties

Correlations between CR for budesonide and SRI, respectively E-280/CSA are shown in Fig. 12. There seems to be no consistency in behaviour for the different types of lactose, neither for SRI nor for E-280/CSA as independent parameters (Fig. 12A and B). Consistency is not improved when the correlations are linked for carrier size fractions with approximately the same mean diameter (Fig. 12C and D). At best, one could suggest that there is an overall tendency for CR to (slightly) increase with increasing SRI and E-280/CSA to a maximal value that is achieved at threshold values of approximately 5 (for SRI) and 1 (for E-280/CSA), respectively. The results confirm that carrier surface properties within the range of variation that can be obtained from standard grades of lactose, are of lower relevance to the performance of adhesive mixtures with 0.4% budesonide in a basic air classifier. In addition to the previously discussed distribution of drug between irregular and smooth carrier sites, this is also a consequence of the type of separation forces generated in such a classifier. For DPIs relying primarily on friction and drag (or lift) forces, carrier surface roughness on a scale larger than the diameter of the drug particles can prevent these forces getting an effective hold of the adhering particles, as shown schematically

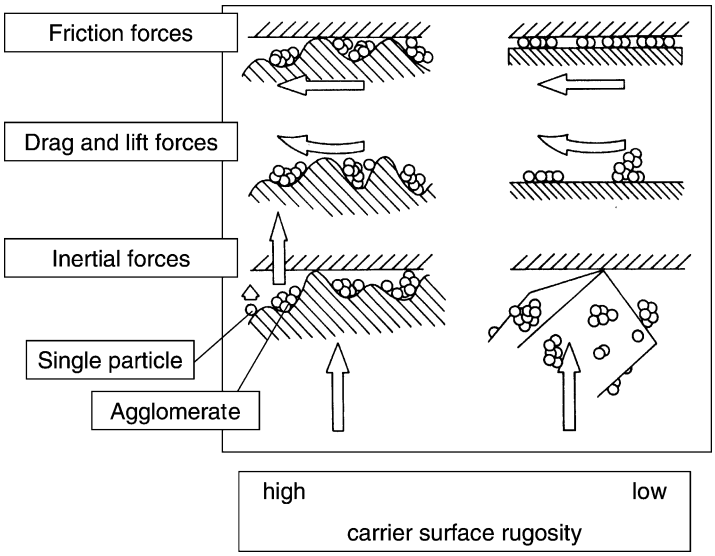


Fig. 13. Schematic presentation of the types of separation forces for adhesive mixtures in dry powder inhalers for two extremes regarding carrier surface roughness.

in Fig. 13. For inertial forces, the surface rugosity is quite irrelevant in this respect. A certain rugosity may even be beneficial for drug detachment in an air classifier. If drug agglomerates with sufficient consistency to be released as a whole are stored away during the mixing process in larger pores, they may already be detached at relatively low impact forces (at low velocities) of the carrier crystal, due to their high inertia. Besides, a certain rugosity can prevent that press-on forces during the mixing process increase the adhesive forces between drug and carrier particles extensively, although this depends on the drug load of the carrier.

In summary, the results presented in Figs. 2 and 8 suggest that there is a decreasing adhesive force between drug and carrier with decreasing mean carrier diameter, although adhesion forces have not actually been measured. This can be explained with an increasing potential for multiple contact points, increased particle contact area (from the presence of ductile peptide and protein layers) and increased number of capillary forces (from the high water contents of these layers) with increasing carrier diameter. Coarser carrier fractions may also yield higher inertial and frictional (press-on) forces during mixing. Our results are in disagreement with part of Podczeck's data (1998a), who found a strongly increasing adhesion force with increasing number of lactose fines in the mixture, particularly for fines having the same approximate size distribution as the drug. For such (lactose–drug) combinations, the type of adhesion is rather that between two spheres than that between a sphere and a flat surface. Theoretically, the force of adhesion between two spheres is proportional to the diameters of both spheres according to the proportionality constant $D = d_d \times d_c/(d_d + d_c)$, where d_c represents the diameter of the carrier and d_d that of the drug particle. This constant has the value of 2 when d_d equals 3 μm and d_c is 6 μm, but decreases to 1.5 when the carrier particle diameter d_c is reduced to 3 μm. Therefore, also for this size range of carrier particles, the force of adhesion should decrease with decreasing 'carrier' diameter.

4. Conclusions

CR experiments with adhesive mixtures containing 0.4% budesonide have shown that the carrier surface properties within the range of variation obtained from standard lactose grades, are of lower relevance to the performance of adhesive mixtures in a basic air classifier, particularly at higher flow rates through the classifier. A quite dramatic change in carrier surface texture appeared to be necessary to obtain only a moderate change in CR, and clear correlations between CR and

SRI or CR and E-280/CSA have not been obtained. A moderate increase in CR with increasing mean carrier diameter (at 30 l/min) can be explained with increasing surface roughness and amount of impurities per unit carrier surface area, as well as with improved flow properties during mixing. Increased carrier surface roughness and impurity may lead to a greater number of multiple contact points and capillary forces as well as increased contact areas between drug and carrier particles. Improved bulk properties may lead to higher press-on forces during mixing, which are most effective for particles that do not find shelter in carrier surface irregularities during carrier particle collisions, however. Therefore, what may seem to be an effect of carrier surface rugosity could well be (at least partially) that of carrier bulk properties. Using a previously introduced FDC to evaluate the obtained CR data at two different flow rates, it can be concluded that particularly the highest adhesive forces in the mixture are increased when coarser carrier fractions are used. These higher adhesive forces seem to be predominantly for the largest drug particles and are not exclusively for particles attached to so-called active sites (in carrier surface irregularities). The observed differences in surface irregularities may not be very relevant to an air classifier at higher flow rates; they can have a great effect on the performance of DPI's relying on other types of removal forces, however. Drug particles in depressions and against steep faces of projections on the carrier surface do not only find shelter from friction and shear forces during mixing. Drag and friction forces can neither get hold of such particles effectively during inhalation.

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