# Chapter 5

## 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 has been studied with a special test inhaler having a basic air classifier for mixtures containing 0.4% budesonide. Carrier crystals were retained in the classifier during inhalation and 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 the surface roughness (measured with nitrogen adsorption) and impurity (expressed as the extinction at 280 nm of a 5% aqueous solution) per unit calculated surface area (CSA) tend to increase with increasing mean fraction diameter for the carrier. Drug re-distribution (over the carrier surface) experiments with two different carrier sieve fractions showed that the amount of drug per CSA (carrier surface payload: CSP) in the state of equilibrium is highest for the fraction with the coarsest diameter. This seems to confirm that carrier surface irregularities are places where drug particles preferentially assemble. However, a substantial increase in surface roughness and impurity appeared to be necessary to cause only a minor increase in the 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. Not only an increased surface roughness and impurity may be responsible for an increase in the adhesive forces between drug and carrier particles when coarser carrier fractions are used. Also bulk properties may play a role. With increasing mean carrier diameter, inertial and frictional press-on forces during mixing are increased too. These press-on forces increase the adhesive forces in the mixture.

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

# 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 fulfil the basic requirements of homogeneous drug dilution and accurate dose metering. The carrier 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 type and magnitude of the adhesive forces between drug and carrier particles depend on a number of different variables (Table 5.1). Some of these parameters also influence the separation forces during inhalation, for instance the degree of fine particle break-up during inhalation. Drug agglomerates attached to the carrier surface have a much higher inertia than single drug particles. Inertial separation forces acting on such particles during inhalation are therefore much higher.

Table 5.1. Some parameters that influence the drug distribution and the adhesive forces between drug and carrier particles in adhesive mixtures.

| Parameter | Reference(s) |
|---|---|
| ✓ Degree of fine particle break-up during mixing | Staniforth, 1987; Aulton and Clarke, 1996 |
| ✓ Drug distribution over the carrier surface (including 'active sites') | Staniforth, 1995; Podczeck ,1999 |
| ✓ Type of interaction force between drug and carrier | Hickey et al., 1994; Podczeck, 1996; Price et al., 2002 |
| ✓ Magnitude and effectiveness of the press-on forces during mixing | Podczeck, 1996 |
| ✓ Mixing conditions (type of mixer, mixing time and speed, batch size) | Zeng et al., 2000b |
| ✓ Physico-chemical properties of drug and carrier | Most references |
| ✓ Size and shape distribution of drug and carrier particles | Hickey and Concessio, 1997; Podczeck, 1998b |
| ✓ Conditioning of the starting materials: | |
| - equilibrium moisture content | Maggi et al., 1999; Price et al., 2002 |
| - electrostatic behaviour | Staniforth and Rees, 1982 |
| ✓ Carrier (surface) payload | Steckel and Müller, 1997 |

Many approaches have been presented to influence or control the adhesive forces between the drug and carrier (or between drug) particles (Table 5.2). They include particle engineering processes for the preparation of special drug and carrier particles. Different size fractions of alpha lactose monohydrate have been investigated as carrier regarding the powder flow from perforated capsules (Bell et al., 1971), the amount and properties of the obtained fine particle fraction (fpf) during inhalation (e.g. 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 to improve the flow properties and the dose consistency (Timsina et al., 1994; Hickey and Concessio, 1997), a positive effect on the fpf from the presence of lactose fines (generally

< 10 μm) in the mixture has been recognised. The effect of adding fine particles to the mixture on drug dispersion during inhalation may dominate over the effects of carrier particle size and carrier rugosity (Zeng et al., 2001a). Lactose fines may be present in the mixture from wear of larger crystals (e.g. during mixing), from selection of lactose grades with wide size distributions, particularly milled lactose grades (Karhu et al., 2000), or from the addition of certain amounts of lactose fines to coarser lactose carrier fractions (Arnold et al., 1995; Zeng et al., 1998; Podczeck, 1998a).

Table 5.2. Methods to influence or to control the adhesive forces between drug and carrier particles in adhesive mixtures for inhalation.

| Method | Reference(s) |
|---|---|
| ✓ Selection of special carrier size fractions | Steckel and Müller, 1997 |
| ✓ Addition of lactose fines to the mixture | Arnold et al., 1995; Podczeck, 1998a |
| ✓ Selection or modification of the carrier surface rugosity (and impurity) | Vanderbist and Maes, 1998; Zeng et al., 2001b; Price et al., 2002 |
| ✓ 'Passivation' of active carrier bonding sites | Staniforth, 1995 |
| ✓ Reducing the adhesive forces in the mixture, e.g. by production of drug particles with: | |
| - super critical fluid technology | Beach et al., 1999 |
| - (co-)spray drying with excipients | Venthoye et al., 2001 |
| - emulsification and freeze-drying | Edwards et al., 1997, 1998 |
| or by adding 'force control agents (FCA's)' | Meakin et al., 1998; Begat et al., 2001 |

*1.2. Carrier surface rugosity*

The effect of carrier surface rugosity on drug dispersion from 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 obtained from crystallisation of spray-dried lactose, reduces the contact area between drug and carrier particles. This was found to improve the inhalation efficiency of the Spinhaler. Several other studies in the past fifteen years have confirmed that the carrier surface rugosity on a micronscale 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., 2000a, 2001a). Carrier rugosity and sites with higher bonding energy have been described in many different ways (Table 5.3). They include small discontinuities of crystal planes, such as clefts, pores, local projections and adhering fines resulting from milling and wear. 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 re-attach them to areas with high bonding 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 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). They may also be the result of standard crystallisation processes (e.g. by coalescence during crystal growth). Different techniques have been proposed to quantify surface rugosity, such as laser profilometry (Podczeck, 1999) and air permeametry (Ganderton and Kassem, 1991; Zeng et al., 2001a).

Table 5.3. Review of terms used to describe carrier surface conditions.

| Term | Reference(s) |
|---|---|
| Surface rugosity (discontinuities) in terms of: | |
| ✓ clefts, grooves, local surface depressions and projections, and adhering fines | Staniforth, 1996 |
| ✓ granular structures | Harjunen et al., 2002 |
| ✓ crystallised amorphous structures | Kawashima et al., 1998 |
| Active sites in terms of: | |
| ✓ adhering fines | Podczeck, 1998a |
| ✓ surface discontinuities | Staniforth, 1995, 1996 |
| ✓ amorphous spots; disorders in crystal structure | 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*

In many different studies, the relevance of surface energetics to the interfacial contact between drug and carrier has been emphasised, e.g. Ahmed et al. (1996), Buckton (1997), Shekunov and York (2002). Partially amorphous or unstable polymorphic forms (as from mechanical size reduction or spray-drying) and changes therein (Harjunen et al., 2002) can 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 surface impurities, like salts, urea, water soluble protein residues and peptides, which are the remains of adhering mother liquor. Their chemical structure is different from that of lactose, which is relevant to the type and size of the adhesive force (for instance 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. These residues may contain water in amounts 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 local water adsorption on the crystal surface. This phenomenon of water concentration in small areas has been termed 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. They may also result in capillary forces between de drug and carrier particles and influence the degree of tribocharge during mixing and inhalation. Recently, some special techniques have been introduced to produce high purity carrier lactose with a high degree of crystallinity and a 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 (summarised in Fig. 5.1) have been investigated separately, possible interactions between these variables have not been studied extensively. Particularly, the influence of the type (and magnitude) of the removal forces on the fine particle fraction from a dry powder inhaler (dpi) is often 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 are attached to a carrier substrate on the adhesion force between the both and found that an increase in press-on force by a factor 2 to 3 may increase the adhesion force by a factor 1.5 to nearly 10, depending on the type of adhering particles and carrier substrate.

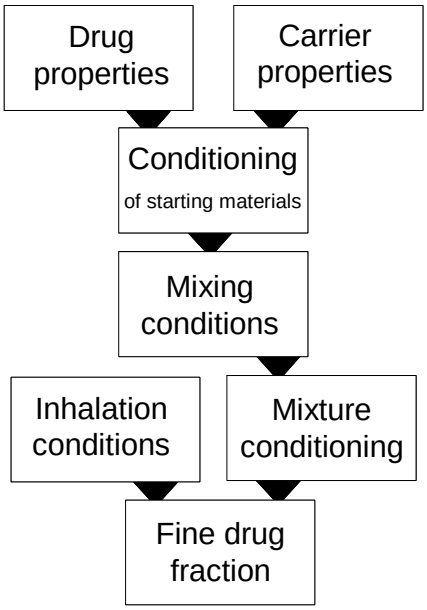


Figure 5.1. Schematic, simplified presentation of the variables that influence the fine particle detachment from adhesive mixtures during inhalation.

The main objective in this thesis is to optimise the balance between the adhesion forces in the mixture and the removal forces during inhalation with air classifier technology as powder de-agglomeration principle. For a better understanding of the parameters that control the adhesive forces in the mixture, the relevance of carrier surface and bulk properties in relation to the carrier size distribution has to be known. In this chapter, the effect of carrier surface rugosity and degree of impurity of standard alpha-lactose monohydrate (Pharmatose) grades on the carrier interaction with budesonide is investigated. 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 by Sofotec (Germany) in a size distribution 10% < 0.54 μm and 100% < 4.60 μm ($X_{50}$ = 1.04 μm) measured with dry laser diffraction analysis. The budesonide was screened through a 90 micron 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). The fractions were prepared in small batches of approximately 100 g by 20 min vibratory sieving (Analysette 3, Fritsch, Germany), followed by 20 min air jet sieving (A200, Alpine, Germany).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.

### *2.2. Carrier characterisation*

Size distributions of all carrier fractions and amounts 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 dry powder disperser at 3 to 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 ($m^2/g$) 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. Because the solutions were clear, filtration was not necessary.

Moisture sorption and desorption isotherms at 25°C of Pharmatose 110M 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 zero relative humidity until the rate of change in weight reached a value smaller than 0.0005 percent per minute. Next, the relative humidity was increased in steps of 10%. The total percent of water uptake (% $H_2O$) for each carrier fraction between 0 and 90 %RH was calculated.

### *2.3. Expression of the results from carrier characterisation*

The 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 introduces 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 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 to 1.05 (CSA corrected for particle shape). The ratio of BET to CSA has been termed surface roughness index (SRI).

*2.4. Adhesive mixture preparation and characterisation*

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 to 20 ml of 100% ethanol and the drug solutions were separated from non-dissolved lactose crystals using a centrifuge (5 min at 3000 rpm; Rotana 3500, Hettich, Germany) and diluted (if necessary) before measuring the drug concentrations with a spectrophotometer at 242.8 nm (PU 8720 UV/VIS, Philips, The Netherlands).

*2.5. 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 Paragraph 2.1. Small amounts (25 g) of these fractions (having different specific surface areas: CSA's) were blended with different amounts of budesonide to obtain mixtures with the same carrier surface payload of approximately 0.12 g/m$^2$ for all fractions. Mixing procedures were the same as described in paragraph 2.4. Next, two different mixtures (containing different carrier fractions) were mixed together for a period of ten minutes in a weight ratio of 1 : 1, starting with the finest (45-63 μm) and coarsest (180-250 μm) carrier fractions. Immediately after mixing, 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 carrier surface payloads in the original carrier fractions, using the same procedures as described for homogeneity testing (paragraph 2.4). Mixing, separation procedures and subsequent carrier surface payload 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 the mean carrier diameters in subsequent experiments. All carrier surface payloads were expressed in gram per CSA.

*2.6. Carrier residue (CR) measurements*

The special test inhaler (CII) with basic air classifier used for the carrier residue experiments has been described previously (de Boer et al., 2003). The test inhaler was connected to a four stage impactor of the Fisons type (Elgebe, The Netherlands) so as to use it under exactly 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. Fine particle fractions were actually measured (as a control value) but they are not presented 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 2 series of 10 inhalations of 25 mg of mixture each. Carrier residue values have been expressed as percent 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. 5.2 shows the results of the budesonide re-distribution experiments. When two drug-carrier mixtures with different carrier fractions from the same batch of lactose with initially the same carrier surface payload (in gram drug per unit CSA) are mixed together for a certain period and subsequently separated by mild hand sieving, it appears that some drug has migrated from the fine towards the coarse carrier particles. When this process of mixing together followed by separation (and analysis of the carrier surface payload) is repeated over longer mixing times, the drug distribution over both fractions seems to reach an equilibrium (which is established already after 30 min mixing time). The ratio of carrier surface payload for the coarse fraction to that for the fine fraction in the state of equilibrium (averaged 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. 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). Obviously, the changes in the carrier surface payload for the coarse carrier fraction are much greater than those for the fine carrier fractions, because of the increasing carrier surface area with decreasing (mean) carrier diameter.

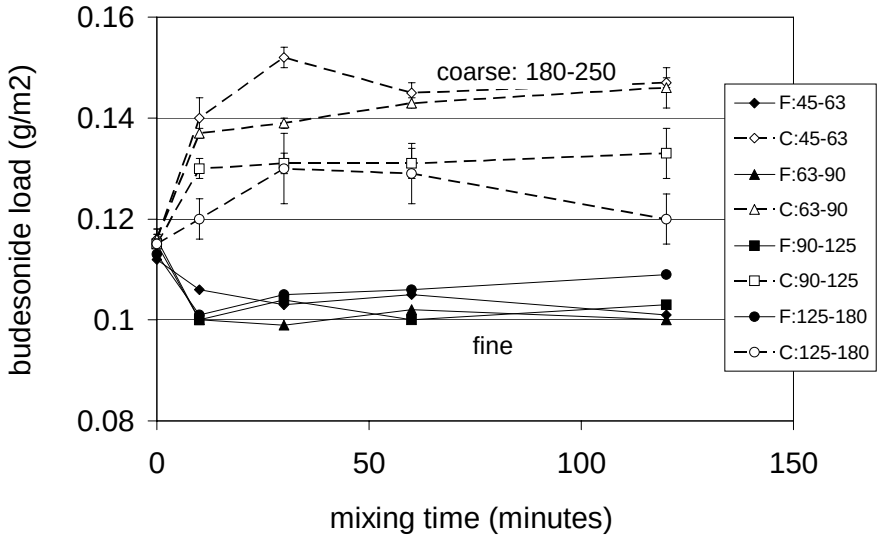


Figure 5.2. Budesonide re-distribution between two carrier fractions (from the same batch of Pharmatose 100M) having different size distributions. The graphs show the carrier surface payload of each fraction as function of the time with another carrier fraction (with initially the same drug load). In all experiments, the coarse fraction was the same: 180-250 μm (discontinuous lines and open symbols). Continuous lines (closed symbols) represent the fine fractions in the mixtures with this coarse fraction. Two fractions mixed together 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 SD in drug load.

Drug re-distribution experiments were undertaken for a better understanding of previous work, which is somewhat confusing and contradictory. 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. In a different study, it was 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 (Podczeck, 1999). In this study, mass median aerodynamic diameters (mmad's) for the fine drug fractions in an Anderson impactor from these mixtures were considerably larger than the mmad of the primary drug particles. Podczeck therefore concluded that the drug is preferentially adhered to the fine lactose monohydrate particles instead of to the coarse crystals. Drug and fine carrier particles form strong agglomerates that are dispersed during inhalation and deposited in the impactor together. Podczeck found support for this explanation by separating the mixtures into two fractions over a 74 μm sieve and analysing the drug amounts in both fractions (coarse and fine). The drug concentrations appeared to be two times higher in the finest fraction for mixtures containing 10 and 20% fines and even three times higher for mixtures with 30% fines.

Although this may not seem so, the results in Fig. 5.2 are in good agreement with those presented by Podczeck (1999) when her values are corrected for the difference in specific surface areas between both fractions. From the known density of α-lactose monohydrate (1.54 g/cm$^3$), the mean Feret diameters for the different fractions in Podczeck's study and the composition of the mixtures (10, 20 and 30% fine lactose), the total surface areas 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 estimated ratio of total surface area for the fine fraction to that of the coarse one (on average for all grades of lactose) is 73 to 27 (equals approximately 3 : 1) for the mixtures with 10% fines and 91 to 9 (equals 10 : 1) for the 30% mixtures. Podczeck (1999) found two thirds of the drug in the fine fraction 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 carrier surface payload (g/m$^2$) was highest in the coarse fractions. Both in our and Podczeck's experiments, it must be assumed that the difference in payload between de fractions (fine and coarse) is caused by a difference in carrier surface properties, and not so much by different bulk properties (press-on forces), because both fractions were mixed together. 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 1.5 to 2 (Fig. 5.2).

*3.2. Carrier surface roughness index (SRI)*

Fig. 5.3 shows that the ratio of carrier surface area from nitrogen adsorption to calculated surface area (defined as surface roughness index: 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. 5.2). It is important to realise 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. 5.4 shows for two different sieve fractions of

Pharmatose 150 M, that none of the crystals has completely smooth crystal planes. Local projections and depressions exist, against or inside which the naturally adhering lactose fines (of approximately the same size as the drug particles) tend to assemble.

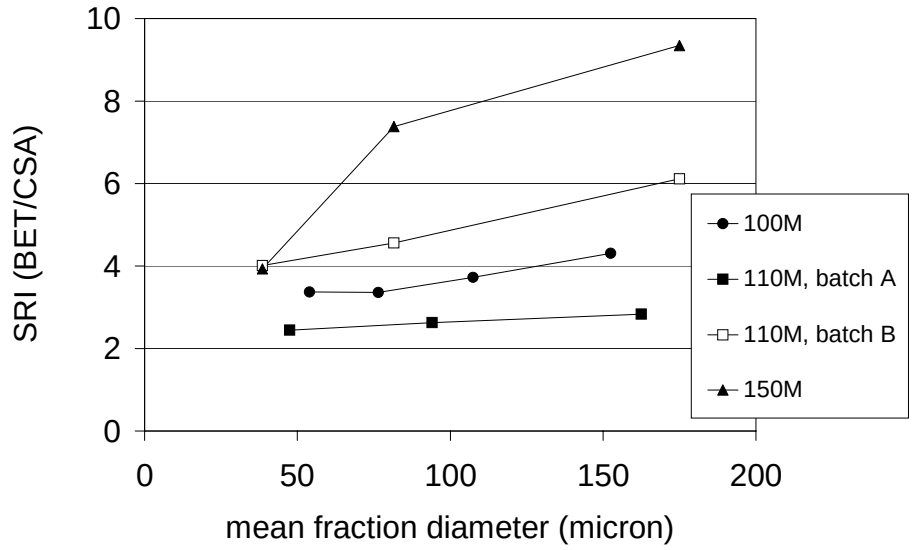


Figure 5.3. Surface roughness index (SRI, equals ratio of BET to calculated surface area: CSA) as function of the mean fraction diameter for fractions derived from various batches of Pharmatose. The lines connect size fractions derived from the same batch. The BET-values used for the calculation of SRI are the mean of six replicate measurements.

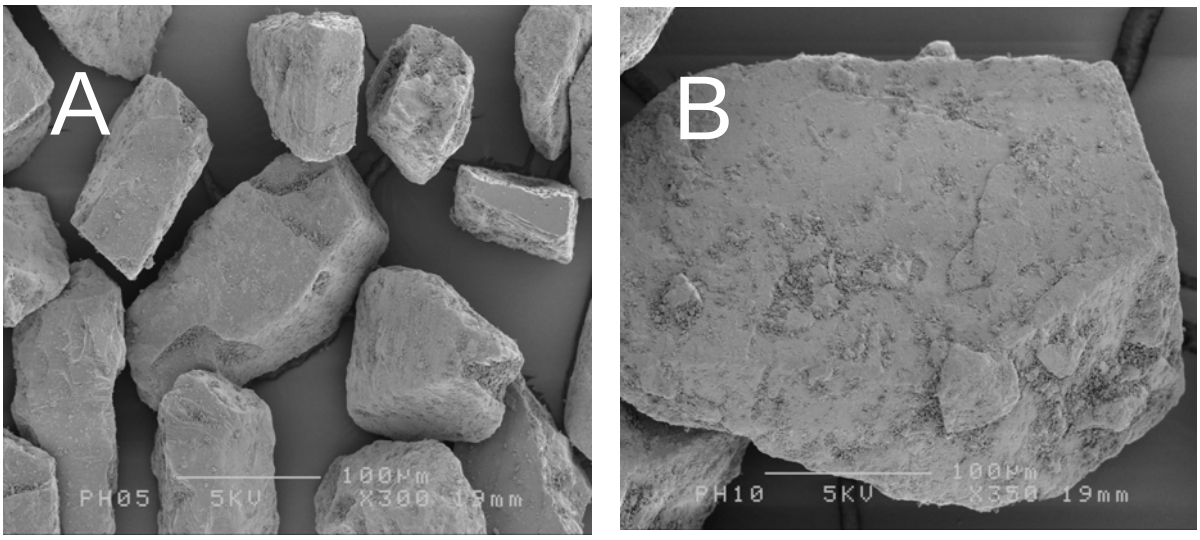


Figure 5.4. Scanning electron micrographs of two different carrier sieve fractions derived from Pharmatose 150 M: 63-100 μm (A) and 150-200 μm (B). Photographic magnifications are 300x (A) and 350x (B).

Fine drug particles show the same tendency (Kulvanich and Stewart, 1987). This gathering of fine particles (of both lactose and drug) is not necessarily a consequence of a higher local bonding energy however. The relatively steep faces of the projecting plateaus on

the crystal surface, as well as 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 when high inertial mixing forces (as in a Turbula type of mixer) are involved.

*3.3. Carrier surface impurities*

Fig. 5.5 shows that the amount of impurities (per unit calculated surface area) increases with increasing mean fraction diameter for the batches in this study also.

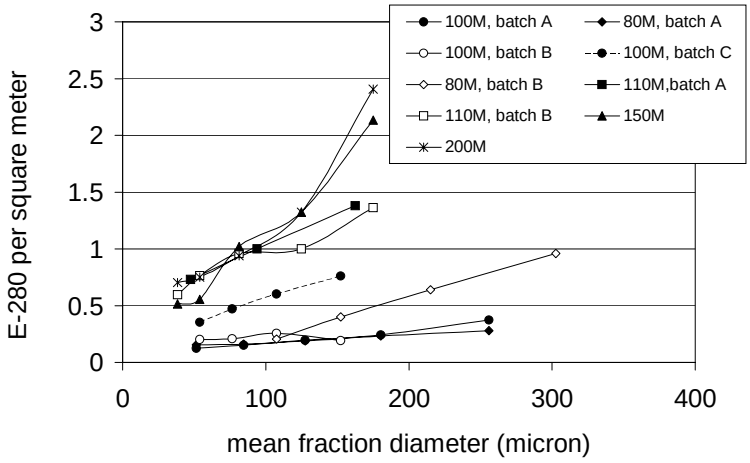


Figure 5.5. Extinction at 280 nm (E-280) per CSA of 5% aqueous lactose solutions as function of the mean fraction diameter for fractions derived from various batches of Pharmatose. The lines connect size fractions derived from the same batch. Each value is the mean of two duplicate measurements performed on two different solutions prepared from the same sample.

Extinction at 280 nm of a lactose solution is primarily the result of the presence of aromatic amino acids (and HMF), which represent 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 sticks to the lactose crystals after they leave the centrifuge, increases with increasing carrier surface roughness. There is also a contribution from minor amounts of urea and riboflavin to E-280. Considering the large amounts of water (> 30%) which can be absorbed by peptides and proteins compared to alpha-lactose monohydrate, it may not be surprising that the percent weight increase per unit carrier surface area (%$H_2O$/CSA in Fig. 5.6) for Pharmatose 110 M (batch B) shows the same trend as function of mean fraction diameter as E-280/CSA (Fig. 5.5). 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. 5.7), 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 only slightly lower. It is highly unlikely that amorphous lactose fractions play a role in respect of drug-to-carrier interaction, because amorphous lactose already crystallises after exposure to relative humidities between 45 and 50% (Vromans, 1987; Buckton and Darcy, 1996).

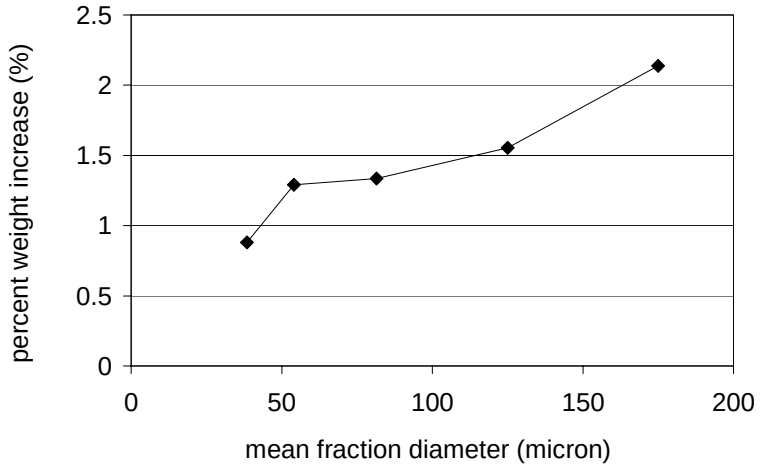


Figure 5.6. Percent weight increase (%$H_2O$) as the result of water uptake between 0 and 90 % RH (25°C) per unit calculated carrier surface area (CSA) as function of the mean fraction diameter for fractions derived from Pharmatose 110M. Each value is the mean from two different moisture isotherms (for two different samples taken from the same fraction).

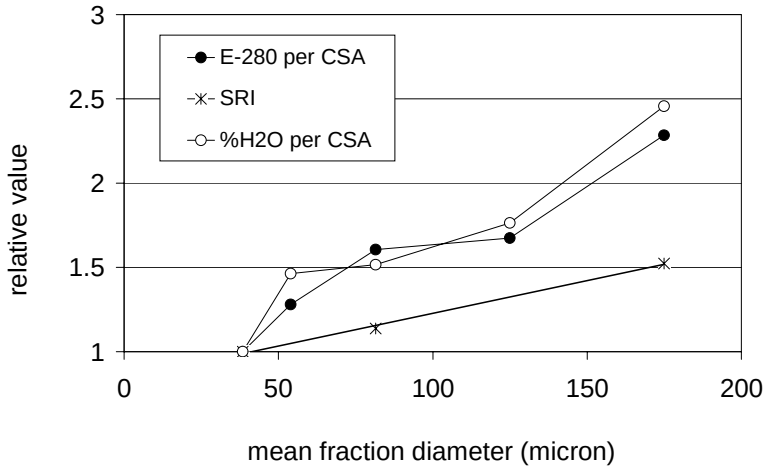


Figure 5.7. SRI, E-280/CSA and %$H_2O$/CSA for different carrier size fractions from the same batch of Pharmatose 110 M relative to their respective values for the finest fraction (32-45 μm). Data derived from the Figs. 5.3; 5.5 and 5.6.

*3.4. Carrier residue (CR) measurements*

The carrier residue at 30 l/min as function of the carrier size fraction for a number of different lactose types is shown in Fig. 5.8. No clear trend can be observed; only fractions derived from two specific batches of Pharmatose 100 and 110 M show an increasing CR with increasing mean fraction diameter, as one might expect from the increasing surface irregularities and impurities. However, it should be realised that the results from inhalation experiments do not solely depend on the adhesion forces in the mixture, but also the magnitude and the effectiveness of the removal forces generated by the inhaler.

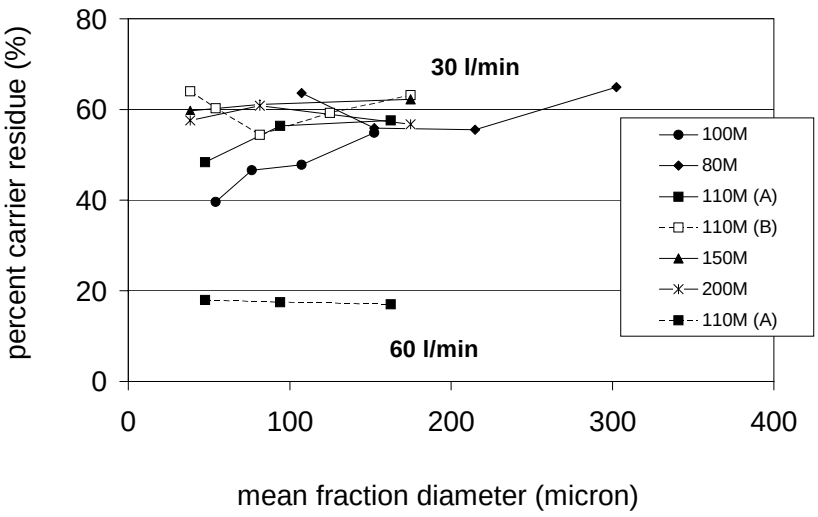


Figure 5.8. Carrier residue (CR) as function of mean carrier diameter for carrier fractions derived from different types of Pharmatose; mixtures with 0.4% budesonide. Test inhaler with basic air classifier; mixing time 10 min; inhalation time 3 s. Each value is the mean of two series of ten inhalations.

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. 5.8 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 carrier surface conditions, which is the reason why most of the experiments were conducted only at 30 l/min. The higher sensitivity at 30 l/min can be explained with a previously introduced force distribution concept (de Boer et al., 2003), as shown in Fig. 5.9.

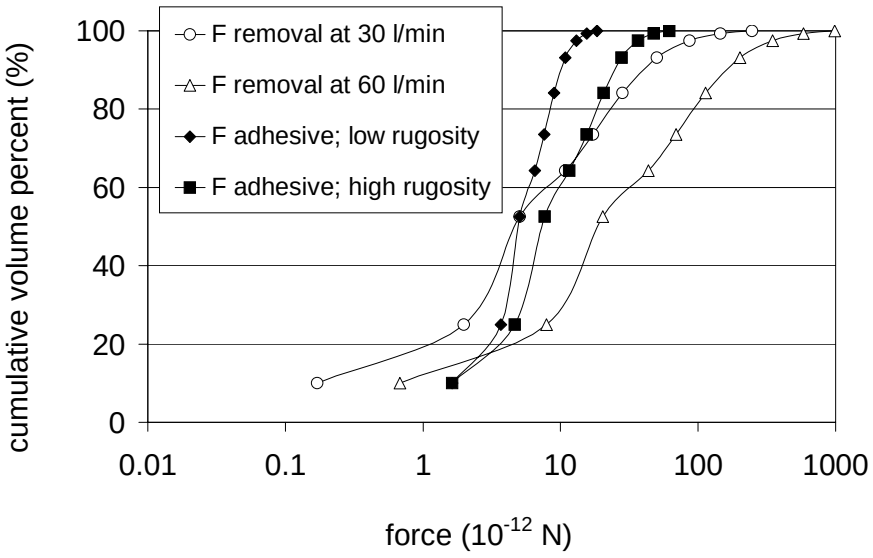


Figure 5.9. Force Distribution Concept: schematic presentation of the size distributions of the adhesive forces in the mixture and the removal forces during inhalation with an air classifier (at two different flow rates). The explanation is given in the text.

The explanation includes that the entire size distribution curve for the generated removal forces (open symbols) shifts to higher force values at higher flow rates through the classifier. As a result, the Y-coordinate for the intersection between both size distribution curves (for adhesive and removal forces) shifts to a lower value, meaning that the volume percent of particles that remains attached during inhalation is decreased. This results in a lower CR. In this range of values for the cumulative volume percent, the distribution curve for the separation forces is least steep (representing the smallest drug particles in the mixture). So, a minor shift of the distribution curve for the adhesive forces in the mixture has little effect on the Y-coordinate for the intersection between both curves within this range of volume percent values. The force values in Fig. 5.9 are fictitious, but the size distribution curves for the forces have realistic shapes, based on the S-shaped cumulative volume percent curve as function of the diameter for the drug from laser diffraction analysis.

The highest adhesive forces in the mixture, mainly applied to the largest drug particles (de Boer et al., 2003), increase more strongly with increasing mean carrier diameter than the lowest adhesive forces by which primarily the smallest drug particles are attached. This could have two reasons as shown in Fig. 5.10.

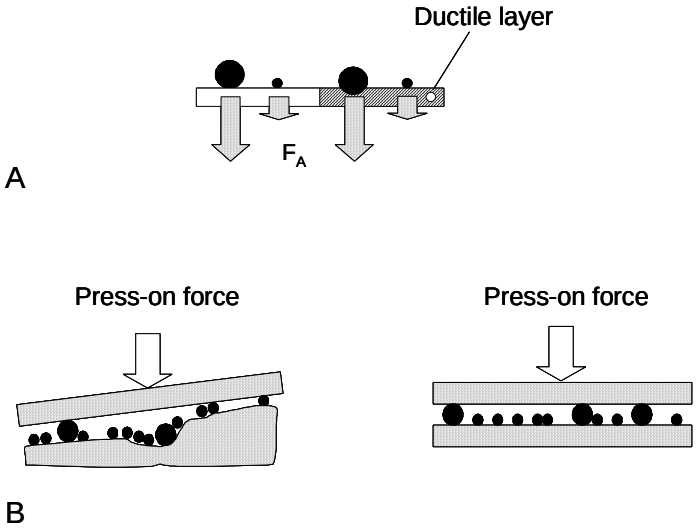


Figure 5.10. Figure explaining why the highest adhesive forces in an adhesive mixture are increased most strongly due to different effects: explanation in the text.

Increasing the mean carrier diameter generally results in a higher degree of surface rugosity and increased amount of impurities (Figs. 5.3 and 5.5). Impurities may be ductile layers. Under the pressure of an adhering particle, such layers may show plastic deformation which increases the contact area with the particle. The largest drug particles are attached with the highest adhesive forces and therefore, they suffer from the highest increase in contact area (Fig. 5.10A). Because of their large size relative to the size of carrier surface pores, large drug particles also have a greater chance of being attached with multiple contact points than smaller ones. Increasing the mean carrier diameter also results in higher press-on forces during the mixing process. As shown in Fig. 5.10B, larger particles may provide shelter from the press-on forces to smaller ones, but the sheltering effectiveness depends on the carrier surface rugosity as well as on the distribution of drug particles over smooth crystal planes and surface discontinuities.

*3.5. Correlations between CR and carrier surface properties*

Correlations between CR and SRI, respectively E-280/CSA for budesonide are shown in Fig. 5.11.

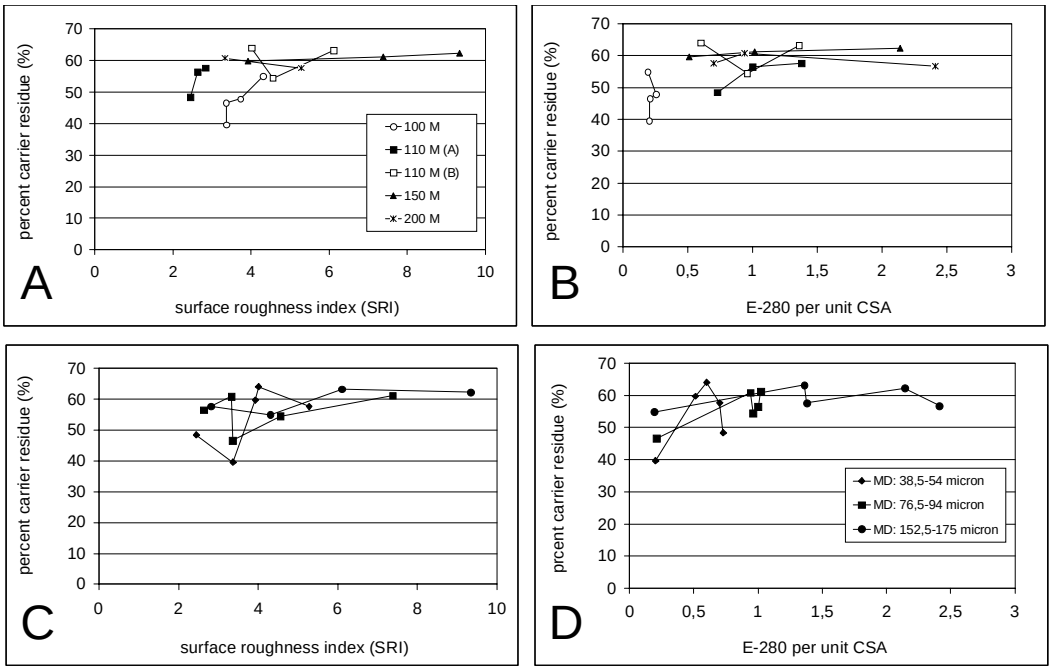


Figure 5.11. CR as function of SRI (A) and E-280/CSA (B) respectively. Linkage is for carrier size fractions derived from the same batch of Pharmatose.
Figures 5.11C and D show the same correlations for CR; linkage is now for carrier size fractions with approximately the same mean diameter (MD).

The correlations are not consistent for the different Pharmatose types, neither for SRI nor for E-280/CSA as independent parameter (Figs. 5.11A and B). Consistency is not improved when the data points are linked for carrier size fractions with approximately the same mean diameter (Figs. 5.11C 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 of 60% (at 30 l/min through the test inhaler used), which is achieved at threshold values of approximately 5 for SRI, and 1 for E-280/CSA respectively. The results therefore indicate that carrier surface properties, within the range of variation that can be obtained from standard grades of lactose (Pharmatose), are of lower relevance to the performance of adhesive mixtures with 0.4% budesonide in a basic air classifier. This is a consequence of the type of (inertial) separation forces generated in such a classifier. For dpi's 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 that these forces get hold effectively of the adhering particles, as shown schematically in Fig. 5.12. For inertial forces, a certain rugosity may even be beneficial however, as this can prevent that press-on forces increase the adhesive forces between drug and carrier particles extensively during the mixing process (although this depends on the carrier payload too). If drug agglomerates (with sufficient consistency to be released as a whole) are stored in larger pores during the mixing process, they may already be detached at relatively low impact forces, due to their high inertia.

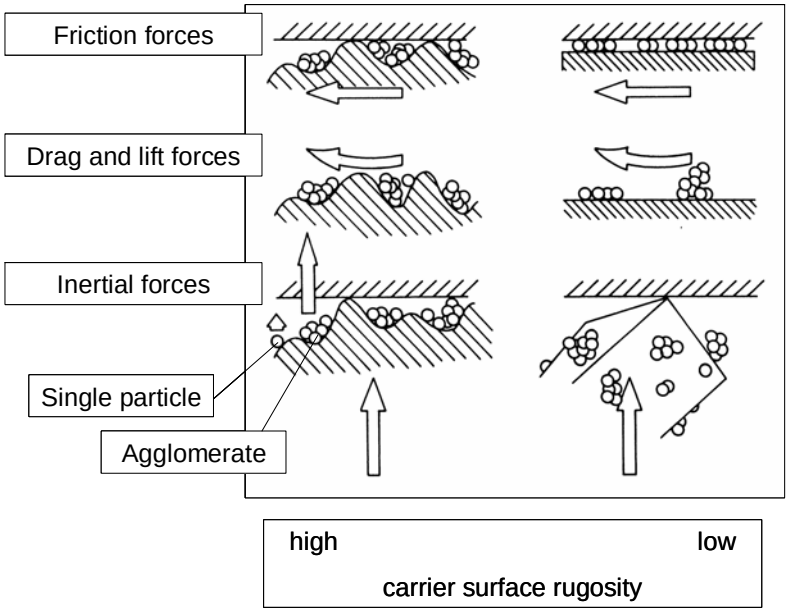


Figure 5.12. Schematic presentation of the effectiveness of different types of separation forces in drug detachment from carrier crystals in adhesive mixtures for two extremes regarding carrier surface roughness.

## 4. Conclusions

Carrier residue 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 to increased contact areas between drug and carrier particles. Improved flow properties may lead to higher press-on forces during mixing, which are most effective for particles that do not find shelter from these forces in carrier surface irregularities during carrier particle collisions. Therefore, what may seem to be an effect of carrier surface rugosity could well be (at least partially) an effect of carrier bulk properties. A previously introduced force distribution concept to evaluate the obtained CR data at two different flow rates, suggests 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 but they can have a great effect on the performance of turbulent shear inhalers, as drag and friction forces can not effectively get hold of drug particles in depressions and against steep faces of projections on the carrier surface.

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