Citation for published version:

de Boer, AH, Chan, HK & Price, R 2012, 'A critical view on lactose-based drug formulation and device studies for dry powder inhalation: Which are relevant and what interactions to expect?', *Advanced Drug Delivery Reviews*, vol. 64, no. 3, pp. 257-274. <https://doi.org/10.1016/j.addr.2011.04.004>

DOI:

[10.1016/j.addr.2011.04.004](https://doi.org/10.1016/j.addr.2011.04.004)

Publication date:

2012

Document Version

Peer reviewed version

[Link to publication](#)

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ORIGINAL TITLE

Interactions, structure and process: relevant aspects of the development of lactose-based formulations and devices for dry powder inhalation

PROPOSED TITLES

Aspects of the development of lactose-based formulations and devices for dry powder inhalation. Which are relevant and what interactions to expect?

A critical view on lactose-based drug formulation and device studies for dry powder inhalation

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Contents

1. Introduction: adhesive mixtures for inhalation
2. Different research focuses
 - 2.1. functionality testing of lactose carriers
 - 2.2. drug and carrier surface properties and interaction studies
 - 2.3. the mixing process: the relevance of carrier bulk properties
 - 2.4. the role of excipient fines
3. The mixing process and carrier flow properties
4. Interactions between variables
 - 4.1. linked effects
 - 4.2. conditional effects
 - 4.3. interacting effects
5. Taking a critical view
 - 5.1. on the role of carrier surface properties
 - 5.2. on the role of amorphous fractions
 - 5.3. on the role of lactose fines
6. The relevance of device design
7. Conclusions
- References

Key words:

adhesive mixtures, carrier lactose, dry powder inhalation, pulmonary drug deposition, powder mixing, dispersion

ABSTRACT

Many years of research have not led to a profound knowledge of the mechanisms involved in the formulation and dispersion of carrier based mixtures for inhalation. Although it is well understood that the mixing is a key process in DPI carrier based formulation, there remains a limited understanding of how blending processes affect in-process material properties and the resulting distribution of the drug in the final dosage form. A great number of variables is considered relevant to the interfacial forces in adhesive mixtures, but their effects have mostly been investigated individually, without taking account of the influence they may have on each other. Interactions may be expected and without proper choices made and definitions given for all the variables involved, conclusions from studies on adhesive mixtures are of less relevance. By varying any of the variables that are not subject of the study, an opposite effect may be obtained. Currently, there is a strong focus on exploring techniques for the characterisation of drug and carrier surface properties that are believed to have an influence on the interparticulate forces in adhesive mixtures. For a number of surface properties it may be questioned whether they are really the key parameters to investigate however. Their orders of magnitude are subordinate to the effects they are supposed to have on the drug-to-carrier forces. Therefore, they seem rather indicators of other variability and their influence may be dominated by other effects. Finally, the relevance of inhaler design is often ignored. By using powerful inhalers, the effect of many variables of current concern may become less relevant. Carrier properties that are considered disadvantageous at present may even become desirable when a more appropriate type of dispersion forces is applied. This can be shown for the effect of carrier surface rugosity when inertial separation forces are applied instead of the more widely applied lift and drag forces. Therefore, inhaler design should be taken into consideration when evaluating studies on adhesive mixtures. It also should become integral part of powder formulation for inhalation.

1. Introduction: adhesive mixtures for inhalation

Powder mixing is the most important unit operation in the preparation of solid dosage forms. It was originally envisaged that mixing of coarse and small quantities of fine particles would pose extra concern regarding attainable homogeneity and the possibility of segregation of the constituents during handling of the blend [1]. However, with the invention of the scanning electron microscope it became possible to investigate these mixtures, and it was recognised that in such mixtures the coarse excipient particles may act as a host for adhering drug particles [2]. Fine particles adhere to the surface of the host crystals by Van der Waals, capillary, electrostatic or mechanical forces and as a result, a higher uniformity of drug distribution in the mixture can be obtained as is theoretically possible on the basis of homogeneity equations derived for random mixtures [3,4]. These findings led to the presentation of a new concept of ‘ordered mixtures’ in powder mixing practice [5]. It was explained that the fundamental difference between an ordered and a random mix is the nature of the forces which limit the freedom of migration for the fine constituent particles within an ordered mixture [6]. The influence of the force of gravity in such mixtures applies to the ordered units and not to the fines within these units. The interaction forces between the drug and excipient host particles were considered beneficial with respect to handling of the powder blend (e.g. for dry granulation, tableting and capsulation) as it significantly reduces the risk of segregation [7-12]. Therefore, early studies focussed on understanding the mixing process [6,13,14]. It was observed that mixing of the same constituents may have different outcomes and this observation showed that mixing of particularly fine and coarse particles is a dynamic process [15]. In an attempt to achieve a better understanding of the different mixture types with their theoretical variances, a ‘total mixing’ concept was introduced [6]. In the same period a debate was started about the correct conception of the term ‘ordered mixture’ and the most appropriate nomenclature for this type of mixture [6,15-22]. In literature, ‘ordered’ was used to refer to mixtures with a high degree of homogeneity in excess of that expected for random mixtures as well as to the new concept described by Hersey. As a response to this confusion, alternative terms were introduced like ‘interactive’ and ‘adhesive’ mixtures. A climax to this debate was given by Staniforth in his British Pharmaceutical Conference Science Award Lecture (1986) in which he explained that in fact all matter interacts irrespective of its nature and size [15]. Therefore, ‘interactive’ is not the correct term to distinguish random mixtures from mixtures in which fine constituent particles adhere to

the surface of much larger coarse constituent particles. Because the latter type of mixture neither guarantees a higher degree of homogeneity than random mixtures, the term 'ordered' has to be rejected too. What matters is that interaction leads to adhesion (or cohesion) which depends on the balance between the interparticulate forces and the force of gravity. Hence, 'adhesive mixtures' is a better name. This reasoning by Staniforth has been adapted, and therefore, the name *adhesive mixture* is used in this manuscript.

Early studies on adhesive mixtures addressed methods to increase the interparticulate forces in the mixture as a high homogeneity was the primary objective and segregation the main concern. Adhesive mixtures were primarily used for tableting and granulation processes. Methods applied to increase interparticulate forces included the use of high energy input mixers, such as ball mills [23,24]. Higher energy input appeared to result in a more rapid mixing and a higher degree of homogeneity. The positive effect of milling was explained by the formation of lattice defects which lead to an increase in surface energy and act as active points for adhesion [25]. Mechanical activation of the carrier surface results in a decrease of the degree of order and this determines the mixing rate. An increase in the adhesive tendency was also reported from applying longer mixing times [26]. The effect was attributed to an increased triboelectrification of the particles in the blend due to an increased number of contacts and collisions between surfaces with longer mixing times.

When adhesive mixtures were investigated for pulmonary drug delivery with dry powder inhalers, the objective changed from preventing segregation to achieving a high and consistent fine particle dose. For this application, the interparticulate forces need to be strong enough to facilitate handling but also weak enough to enable separation of drug and excipient during inhalation, using the air flow through the inhaler device as energy source. Controlling, rather than maximising the interparticulate forces became the new challenge. This required a better understanding of the type of forces involved and knowledge of the factors that influence these forces. Studies were focussed on drug and carrier surface properties, carrier bulk properties, the presence of naturally occurring fines in carrier products and their effects on the distribution of the drug over the carrier surface and the interaction between the both. Many of the properties investigated relate strongly to the carrier particle size distribution, which also affects the flow properties of the carrier. This resulted in functionality testing of commercially available carrier products. Drug mixtures

with these carriers were tested upon consistency of delivered dose and fine particle dose which are determined by the efficacies with which the dose compartment is emptied, the powder is dispersed in the air stream and particles are de-agglomerated during inhalation respectively.

Conclusions from many studies undertaken to understand the drug-to-carrier interactions and the variables that control or influence these interactions are based on the same end parameters, which are the in vitro deposition results or fine particle dose. It should be realised that these end parameters are the net result of a series of subsequent processes which comprises selection (including classification and/or conditioning) or production (including particle engineering) of the starting materials (drug and carrier), the mixing process, dispersion and de-agglomeration in the inhaler device and finally the aerosol characterisation. Each of these operations influences the outcome and it is surprising that in many studies on adhesive mixtures for inhalation the role of the mixing process is neglected. Likewise, the influence of the type of inhaler on the end parameters is often ignored. Different mixer types and inhalers with different dose systems and dispersion principles have been used in various studies. In some studies mixing times, batch sizes and flow rates through the inhaler have not even been mentioned. Not to mention that in most studies the effect of a single variable has been investigated without considering its effect in relation to the influence of all other factors or dependence of the specific properties of the variable thereon. Therefore, conclusions drawn from a particular study may apply only for the conditions chosen. Finally, a tremendous amount of energy has been focussed on studying carrier properties of which their relevance to the drug-to-carrier interaction may be considered doubtful, simply because the order of magnitude of their influence is questionable, or because they are linked to, respectively dominated by other variables.

The aim of this manuscript is first to review and next to take a critical view on the relevance of some of the most extensively investigated carrier properties and to discuss the importance of some neglected operations (mixing and dispersion) in studies on adhesive mixtures for inhalation. Additionally, some examples will be given of variables of which the effect on drug particle release during inhalation seems well understood, but in fact appears to depend on choices made for the other variables or specific properties of the variable in question. Therefore, their effect can even be made opposite

2. Different research focuses

A large number of studies has been undertaken on the subject of adhesive mixtures for inhalation. They can roughly be divided into four different research areas which are briefly reviewed to show the variation in approaches and techniques currently used for drug-to-carrier interaction studies. A critical view on some of these techniques will be given in the chapters 4 and 5.

2.1. Functionality testing of lactose carriers

Pharmaceutical companies have an interest in designing or obtaining the rights to inhalation devices which can be used for a wide range of different drug formulations [27]. The dry powder inhalation products for these inhalers are developed using either catalogue (off-the shelf) carrier products or tailor-made carrier material, such as special size fractions which are processed to fit the device and formulation characteristics. The required carrier properties depend on the type of drug to be processed, the drug concentration (% w/w) in the mixture as determined by the drug dose and the amount of powder to be measured by (or into) the dose system, and the type of mixing process used. They reflect on the emptying of the dose compartment and the dispersion of the formulation during inhalation which determine the consistency of delivered dose and fine particle dose. Carrier excipients furthermore need to be accepted by regulatory authorities, be pure, stable and available from more than one supplier, exhibit no batch or supplier variations and be preferably fully characterisable for parameters known or expected to be relevant to their performance [27]. However, not knowing the precise mechanisms of interaction between drug and carrier particles and all the parameters that influence these interactions in detail, exact specifications for these parameters can not be given. The relevance and precise mechanism of action of most parameters is still uncertain. Therefore, in most cases formulation of adhesive mixtures for inhalation in practice is still an empirical process. Different carrier products with different properties regarding size distribution, surface rugosity and anomeric composition are subjected to functionality testing in order to decide which one has greatest potential for the drug formulation to be used in combination with the inhaler(s) selected for administration [28-31]. Although such focussed-in-house studies are very important for understanding the performance of marketed carrier products in one particular type of inhaler device, they do not result in widely applicable conclusions.

Between two different carrier products many variables regarding particle size and shape distribution, presence of fines and impurities, rugosity, carrier surface payload, etc. are different. This makes it impossible to relate the effect of single physical carrier properties to the aerodynamic behaviour of the mixtures prepared with these carriers [32-33].

Besides, the performance of the optimal formulation in the study may be completely different in another inhaler.

2.2. Drug and carrier surface properties and interaction studies

A review on interparticulate (adhesion and cohesion) forces in adhesive mixtures for inhalation has been published previously [34]. These interfacial forces have been discussed in conjunction with particle preparation techniques such as milling, condensation, spray drying, precipitation and crystallisation which yield different particle surface properties that may directly affect the drug-to-carrier interaction [35]. The recognition of the complex relationship between the physical lactose carrier properties and the aerodynamic drug properties [32] has resulted in a desire to obtain a better understanding of the underlying mechanism(s). This search has stimulated research towards variables that are expected to influence the interparticulate forces and exploring techniques that can be used to qualify and quantify these variables. The existence of carrier surface areas with high surface energy was described to which drug particles are preferentially attracted [36]. These so-called ‘active sites’ have been explained in terms of adhering fines [37], amorphous spots and disorders in the crystal structure [38], impurities [39-40], water of adsorption [39], clefts or asperities [36] and sites of high surface energy [41]. It could be shown that some of the surface properties relate to each other [40]. For example, the carrier surface impurities characterised with the light extinction of a 5% aqueous lactose solution at 280 nm (E-280) and the percent of water of adherence, both per unit calculated carrier surface area (CSA), increase with increasing mean carrier diameter for particles from the same batch of alpha lactose monohydrate (Fig. 1A). This is the result of an increasing size of the carrier surface discontinuities with increasing particle diameter (Fig. 1B) which can be expressed as Surface Roughness Index (SRI: being the ratio of specific surface area from nitrogen adsorption to calculated surface area, Fig. 1A). There may be a simple explanation for both figures since flaws in the crystal lattice at the exterior of the crystal grow with the diameter of the crystal. This results in a more or less constant ratio between the size of the surface discontinuities from lattice faults and the size of the crystal (Fig.

1B). When the crystals are removed from the crystallisation tank, higher amounts of mother liquor remain in these larger surface discontinuities, which after drying of the crystals result in higher amounts of impurities (per CSA). Taking into account that peptide and protein like impurities can absorb much higher amounts of water than alpha lactose monohydrate, it can be explained why the SRI, E-280 and % H₂O all exhibit the same trend with increasing carrier diameter.

The understanding that surface properties play a dominant role in the drug-to-carrier interaction has led to the exploration of a great variety of techniques to measure these properties. They have been reviewed before [42] and include for instance inverse gas chromatography (IGC), X-ray microanalysis, atomic force microscopy (AFM), scanning electron microscopy (SEM) in combination with image analysis, laser profilometry, differential scanning calorimetry (DSC), micro-calorimetry, and dynamic vapour sorption (DVS). A disadvantage of some of these techniques (AFM and laser profilometry) is that only a very small part of the entire carrier surface area can be characterised, whereas particles with large surface discontinuities (e.g. granular structures) can not be measured at all with AFM. On the other hand, AFM delivers directly the force of adhesion between a particle, attached to the cantilever, and a substrate. This also enables a measure of the separation energy necessary to detach a particle from the substrate surface [39]. AFM measurements have been used to show that the separation energy for a drug particle attached to an atomically smooth lactose surface increases with increasing relative humidity to which a lactose surface has been exposed [39]. The rather extreme effect of humidity on the adhesion force and separation energy for salbutamol sulphate-lactose and budesonide-lactose combinations is not reflected by the effect of humidity on fine particle fractions for these combinations from inhalers however. With the same technique, it was shown that increasing the rugosity of a lactose surface widens the distribution of adhesion forces with a drug particle [43]. One of the practical problems to solve in AFM measurements is the uncertainty about the real contact area between the probe and the substrate surface. This makes comparative evaluation of cohesive and/or adhesive forces between different substances onerous. Therefore, techniques were presented to improve the comparability between different drug-excipient combinations, e.g. by the preparation of small spherical polycrystalline particles in a narrow size distribution to reduce the variation in contact area [43]. In another approach a series of different probes with

different contact areas was used to measure the cohesive (X to X) and adhesive (X to Y) force between the same materials repeatedly, yielding different (corresponding) values for both forces from each probe to be plotted in a cohesion-adhesion graph [44]. This technique has led to the presentation of a so-called cohesion-adhesion balance (CAB) from which rankings for the cohesive and adhesive forces of different drug-drug and drug-excipient combinations were derived. This approach has been used to predict the dispersion mechanisms and *in vitro* deposition performance of various drug-carrier combinations [45-46], including ternary mixtures with excipient fines [47]. It could be shown that drug-carrier combinations in which the cohesive component is more dominant than the adhesive tend to yield higher fine particle fractions. This seems logical as a high CAB-value increases the agglomeration tendency of the drug particles and agglomeration increases the ratio of detachment force to adhesion force. An important conclusion drawn from CAB studies is that the balance of cohesive and adhesive forces is highly dependent on the process history of the drugs from the source of the primary crystals, the energy input during comminution and the relaxation behaviour of the mechanically activated drugs. This dynamic change in interfacial behaviour of a drug substance has made controlling drug-carrier interactions difficult using current industrial processing technologies for the drug. To overcome these limitations drugs may need to be conditioned under controlled environmental conditions or exposed to suitable organic vapours to expedite the rate of mechanical relaxation. On the other hand, it can be shown that variations in the CAB can be widely overcome by using highly effective inhalers.

The understanding that carrier surface heterogeneity exists has increased the desire to characterise the entire carrier surface. Techniques like inverse gas chromatography (IGC) were introduced to measure the distribution of surface energy [41]. Studies presenting data from IGC measurements are still relatively scarce however, particularly those in which the surface energy of carrier materials is related to drug adhesion onto the carrier surface. Values presented for the surface energy of lactose have the order of magnitude of 40 to 50 mJ/m² depending on the lactose preparation technique and the size fraction [41,48,49]. Milling causes an increase in dispersive surface energy which is attributed to the formation of amorphous regions [50]. When the amorphous fraction in milled lactose is re-crystallised by exposure to a high relative humidity, the surface energy decreases to the value of the starting material but the energy distribution remains much lower. Both sieved

and milled lactose have broader energy distributions than re-crystallised lactose. For sieved lactose this is explained with a heterogeneous distribution of impurities over the lactose surface and variations in anomeric composition, whereas for milled lactose small amorphous regions would be the reason. The addition of lactose fines may result in a more homogeneous surface energy of lactose particles [49]. Studies presenting correlations between surface energy and dispersion behaviour are scarcely available and they have been given for formulations with (co-processed) rifampicin, salbutamol sulphate, salmeterol xinafoate, ipratropium bromide and co-spray dried cromoglycate [48,51-53]. Clear and unique relationships are often not obtained however [53,54], unless individual data points are eliminated from the comparison [48]. This suggests that general conclusions for the effect of surface energy on drug aerosolisation during inhalation may not be possible as too many other physical variables control or even dominate dispersion [55].

2.3. The mixing process: the relevance of carrier bulk properties

Particle processing, mixing and dispersion are the key operations in adhesive mixture preparation (and testing) for inhalation. It is surprising that particle processing (and characterisation) has received a tremendous amount of attention whereas mixing and particularly dispersion have been rather neglected. This is the reason why these items have been given separate chapters in this manuscript to make up for such omissions. Only one particular aspect of the mixing process is reviewed in this chapter, which is the effect of inertial and frictional forces during the mixing process. During mixing, carrier particles collide with each other and with the walls, blades or impellers of the mixer. The powder flow in a mixer also causes friction forces between the carrier particles. Such inertial and frictional forces are responsible for breaking up natural drug agglomerates. It has been shown that naturally occurring drug agglomerates may be quite strong, at least strong enough to withstand partially break-up in an effective dry powder disperser (RODOS, Sympatec Germany) at relative high pressures of 50 kPa [56]. Pressures of 300 kPa or more may be necessary to obtain the primary particles. It has also been shown that the same drug after mixing with carrier particles may still partially exist as agglomerates, but these agglomerates appear to be weaker than the original ones. They can be broken up into almost primary entities already at a relatively low pressure drop of 4 kPa in a classifier based test inhaler. The size of the drug agglomerates in the blend appears to depend on

particle-carrier interactions and the carrier size fraction they are mixed with [56]. It is not clear whether these are weaker agglomerates in the mixture or are weakened fragments of the original drug agglomerates or newly induced ones during the mixing process. The inertial and frictional forces are also responsible for drug distribution over the entire carrier surface. In the beginning of the mixing process drug particles are randomly distributed over the carrier particles and they tend to be wiped together in carrier surface discontinuities. Spreading over the carrier surface also means a re-distribution from sites with lower adhesion force to sites with higher binding capacity. The rate of distribution of drug particles over the carrier surface depends on the drug concentration in the mixture [57]. When the concentration is low, re-distribution is less effective as particles inside the carrier surface discontinuities find shelter from the inertial and frictional mixing forces. These forces may also change the magnitude of the interparticulate (adhesion and cohesion) forces in the mixture. It has been shown with a centrifuge technique that the force with which particles adhere to a substrate surface depends on the force with which the particles are pressed against this surface [58,59]. The increase of the adhesion force under applied press-on force can be attributed to an increasing contact area as the result of plastic deformation and/or local fragmentation at the contact point. Also the distance between the particle and the substrate surface may be decreased by smoothing out the surface roughness [58]. It could also be shown that the ranking of adhesion forces may be changed, as the increase rate for these forces with increasing press-on force may be different for different particle-substrate combinations [59]. It may not be necessary to mention that repeatedly exerting the same force, as during mixing, has the same effect as increasing the press-on force.

The order of magnitude for the inertial and frictional forces during mixing depends on a number of different variables, such as the carrier particle size distribution, the type of mixer used, the mixing conditions, the batch size and the filling degree of the mixing container. The efficacy of the forces depends particularly on the drug concentration in the mixture. To emphasize the effect of the inertial and frictional forces coarse carrier fractions can be used. The effects mentioned in this chapter are elucidated in the **Figs. 2A-C**. **Figure 2A** shows the residual drug on carrier (carrier residue: CR) after a dispersion test as percent of the initial carrier payload for three different carrier fractions at 30 L/min as function of the amount of drug in the mixture. The data were obtained with a classifier

based metal test inhaler which retains the carrier crystals, thereby making them available for chemical analysis of residual drug on their surface after a dispersion test [60]. At low carrier payload carrier residues are high for all carrier fractions, as the number of carrier sites with high binding capacity is large compared to the number of drug particles in the mixture. When the carrier payload is increased, the excess of drug particles relative to the number of strong binding sites increases and more drug particles become attached with weaker forces and are thus more easily detached during the dispersion test. A higher drug concentration also increases the agglomeration potential which allows greater drug detachment from the carrier surface due to an increased detachment force [61]. However, at a drug concentration in the mixture of approx. 1.0% the carrier residue reaches a minimum value for coarse carrier fractions and a plateau value for intermediate fractions. This is the concentration at which carrier surface discontinuities are saturated and drug particles can no longer find shelter from the inertial and frictional forces during the mixing process. Above these concentration drug particles become exposed to these mixing (press-on) forces which has the consequence that the interparticulate forces in the mixture are increased and so is the carrier residue. The end value for CR at high carrier payloads depends on the order of magnitude for the press-on forces which obviously is highest for the coarsest carrier fraction [60]. The [Figs. 2B and C](#) underline the idea that the efficacy of the inertial and frictional forces depends on the drug concentration. At a low drug concentration (0.4%) in a coarse carrier mixture (250-315 μm) there is a relatively great effect of the mixing time on the carrier residue ([Fig. 2B](#)). The effect is greatest at higher flow rates (≥ 40 L/min). Due to the low efficacy of the inertial and frictional forces in redistributing drug particles from sites with lower binding force to sites with higher binding force, almost all particles can be detached from the carrier after short mixing times at 60 L/min or higher. It requires relatively long mixing times to obtain a high degree of occupation of these sites with higher binding potential, which is expressed in an increased carrier residue at these higher flow rates. At low flow rates, when primarily particles from weaker carrier binding sites are detached, the effect of mixing time is less noticeable.

A payload of 4% on a coarse carrier fraction is theoretically sufficient to expect a multiparticulate (3-fold) drug layer around each carrier particle. This complete carrier coverage with drug particles implies that most active sites are occupied already in the early phase of mixing. The effect of the inertial and frictional forces during mixing is therefore

primarily confined to increasing all interparticulate forces in the blend, which appear to be maximal already after approx. 5 minutes mixing time. This effect is best noticeable at low flow rates: CR of 4% mixtures up to 25 L/min is higher than that for 0.4% mixtures for all mixing times (Figs. 2B and C). It should be mentioned that CR is a relative parameter. CR at 60 L/min is lower for 4% mixtures than CR for 0.4% mixtures. In absolute sense, residual drug per unit carrier surface area (g/m^2) is higher for 4% mixtures [57], and this appears to be independent of the type of drug investigated. It should also be mentioned that the explanation given for the Figs. 2B and 2C has been simplified. In reality, the situation is more complex, as drug particle agglomeration plays a role too and a continuous multiparticulate coverage of the carrier crystals with drug particles is not achieved. From scanning electron micrographs it is known that certain areas of the carrier surface (at the edges of crystal planes) remain quite clean, whereas thicker layers of drug may be present in depressions or around elevations on the carrier surface respectively.

2.4. The role of lactose fines

The positive effect obtained from combining micronised drug particles with a mixture of coarse and fine excipient particles on the dispersion properties of inhalation powders has been described quite early [62]. In this patent different weight ratios and different size ranges for the fines were claimed to increase the *in vitro* deposition of the drug from blends with coarse excipients. Many studies on the effect of fines have been completed since and they were quite recently reviewed extensively [63]. Different excipient particles can be used. Either they are of the same material as the carrier particles (mostly alpha lactose monohydrate), or they are of a different nature, like the sugars glucose, mannitol, sorbitol and trehalose. Different amounts and different particle sizes for the fines have been used and also different mechanisms of action have been proposed, which have been categorised into two main hypotheses [63]. The fines either occupy carrier surface areas of high adhesion or they tend to co-agglomerate with the drug particles on the carrier surface. Supporting evidence exists for both mechanisms but also contradicting conclusions can be found in literature. As support for the occupation of strong carrier bonding sites by added fines, the influence of the blending order has been mentioned. Mixtures in which the fines are mixed with the coarse carrier particles first before the drug particles are added may show a better dispersion performance than mixtures for which the mixing order is reversed, although the effect depends on the total mixing time [29]. This so-called

corrosion or passivation of active sites by sequential mixing is a practical application of an invention by Staniforth [36]. Support for the mechanism of co-agglomeration is primarily obtained from SEM investigation [64]. Due to the conflicting findings, many aspects regarding the influence of fines on dispersion behaviour remain unclear. In general carriers containing greater proportions of intrinsic fines seem to have a better performance, and the optimal median diameter for the fines may be in the range of 5 to 8 μm [63]. In contrast to these conclusions drawn, no recommendations can be given for the concentration of fines in the mixture, nor for the preferable material they should exist of.

3. The mixing process

Powder mixing is one of the most critical processes in the DPI carrier based formulations, as the aerolisation performance is dependant not only on the formation of an adhesive mixture, but also on the liberation and distribution of the drug onto the carrier and the interfacial forces acting between these contiguous surfaces. Considering its significant role, there remains a limited understanding of how blending processes affect in-process material properties and the resulting distribution of the drug in the final dosage form.

Within the industry, blending protocols are empirically researched for each specific type of blender and are optimised across the scales, from lab to full production, to create the desired properties in the final blend. The blending parameters at the production scale are tightly constrained to limit batch-to-batch variability and to achieve the requirements of the final product, such as blend homogeneity, emitted dose and the fine particle dose. Even with these controls in place, mixing remains a significant source of variability within the manufacturing process.

Unlike fluid mixing, where molecules randomly diffuse around from locations of high to low concentrations, powder particles require motion to be imposed on them to initiate mixing. Thus, all powder mixers need to induce motion either by rotational movement of a container or the movement of an impeller within the powder. Historically, two different type of batch processing blenders have been used to mix carrier based DPI formulations. These are tumbling based blenders (e.g. turbula, V-blenders) and high speed impeller mixers. These two mixing processes exhibit a different range of energy inputs, which may

have a critical effect on the blending dynamics and the adhesive properties of the drug to the lactose.

The key mode of operation of a powder mixer is to generate mechanical stress to effectively deagglomerate the cohesive drug. High stresses are needed to break up the agglomerates so that individual particles can be liberated to mix and distribute over the surface of the carrier. Powder mixing is achieved via a combination of different mechanisms, namely convective, diffusive and shear mixing. Whilst all three mechanisms are likely to occur in a mixing operation, which one predominates will depend on the type of mixer, conditions (fill weight, % loading and speed) and the flow properties of the lactose. The only mechanism capable of generating the level of stresses required for deagglomeration of cohesive drug particles is shear mixing. Shear can be generated, for example, in a tumbler mixer along the layer of powder avalanching along a slip failure plane, or in a high shear mixer by the stresses created by the impeller rotating at high speeds within the powder.

For low shear tumbler mixers, the main processing factors are mixing time (Fig 2A) and mixing speed. Both of these factors have been shown to influence the adhesion between drug and lactose particles (Ref 65: Rob). For high shear mixers, the main process parameters of fixed blade geometry blenders is the rotational velocity of the impeller (n_{rpm}) and mixing time (t) (12). In addition to these variables, the torque required to turn the impeller in the powder mix can be continually measured to determine the energy input (E_{in}) to the powder by the impeller via:

$$E_{in} = \frac{\pi \tau t n_{rpm}}{30} \quad (\text{equation 1})$$

where τ is the torque (Nm).

Increasing the energy input in a high shear blender has been shown to directly impact the particle size distribution of the lactose and particulate interactions and, thus, may have a pronounced affect on product performance (Ref. 66 Rob). Bridson et al have shown that the energy input and the design of the impeller had a significant effect on the particle size

distribution of coarse lactose. They found that with increasing input energy there was a loss of lactose fines. They also found that the conditions of storage of lactose prior to blending directly affected the outcomes of the post blending PSD of lactose. These factors will directly affect the flow and fluidisation behaviour of the resultant DPI blend. Begat et al compared the effects of impeller speed and input energy on the structure and aerosol properties of carrier based DPI formulations (Ref. 67: Rob). Their data indicated that the different blends exhibited variations in blend structure with respect to the presence of drug agglomerates and the distribution of the drug on the carrier. Furthermore, increasing the input energy of the mixer by either increasing the impeller speed or the mixing time indicated that higher input energy decreased the fine particle dose of the drug, suggesting that the increasing the input energy of the mixer may increase the adhesive forces in the blend.

There is an increasing trend within the industry to adopt a quality by design (QbD) approach for innovative process manufacturing and quality assurance. While there remains a paucity of data, in the literature, on the correlation between mixing parameters, formulation structure, interfacial forces and aerosolisation performance, advances in the science of powder mixing will be limited. This lack of knowledge limits the move of a paradigm of testing quality in post manufacturing to designing quality during process manufacturing. The introduction of imaging and monitoring technologies within processing mixers may provide some useful insight into the optimum conditions for efficient deagglomeration of cohesive drug during powder mixing and formulation structure. However, these chemical based imaging techniques may not ultimately provide the critical information on the effects of blending on the functionality of the final product.

4. Interactions between variables

It is now fully understood that the fine particle fraction obtained from adhesive mixtures during inhalation depends on a great number of variables relating to the drug and carrier particle properties as well as to the mixing process. Yet, the relevance of some major determinants is still often ignored. They include for instance the carrier payload with the drug, the dispersion process (particularly, the type of de-agglomeration forces applied) and the aerosol characterisation technique. These parameters can change the outcome of a

study completely or result even in opposite conclusions when being chosen differently. Some examples are given in this chapter. Therefore, a major challenge for future research is to investigate for which variable(s) the effect(s) depends on:

- ✓ linkage to other variables (*linked effects*),
- ✓ a specific quality or property of the variable (*conditional effects*), and/or
- ✓ the choice made for one or more of the other variables (*interacting effects*).

4.1. Linked effects

Figure 3 shows a scheme of the most relevant variables and the way in which they can influence each other. Each of the variables mentioned represents several properties, like for instance size and shape distribution, water content, hygroscopicity, anomeric composition and surface rugosity of the drug and carrier particles. **Figure 3** also shows an example of linked effects (indicated with black arrows). When the size distribution of the carrier particles is changed, the carrier surface (scale of rugosity and amount of impurities per unit carrier surface area: see par. 2.2) and bulk properties become different. Also the carrier surface payload with the drug particles (gram drug per square meter carrier surface) is changed. This can have an effect on the degree of saturation with drug particles for the carrier surface discontinuities and the strongest carrier bonding sites. A change in the bulk (flow) properties may cause a change in the order of magnitude for the inertial and frictional forces during the mixing process. This all can influence the efficacy with which drug agglomerates are broken down (or softened) and/or newly induced, drug particles are (re-)distributed over the carrier surface and cohesive and adhesive forces in the mixture are increased during the mixing process (par. 2.3). Obviously this reflects on the mixture properties. Changing the carrier flow properties may also have an effect on emptying of the dose system of the inhaler used, whereas circulation and residence time of the powder in whirl chamber, cyclone or classifier based dispersion systems may become different too. The net effect of all these changes may be a different fine particle fraction but the contribution of each of the linked variables individually to this net effect can not be assessed properly. It is therefore paramount that the effects of variables are investigated in a carefully defined context of all the other parameters that may have an effect on the fine particle fraction.

4.2. Conditional effects

An example of a conditional effect is the influence of carrier particle surface rugosity on the drug particle attachment to the carrier surface and dislodgment during inhalation. Early studies learn that the redispersion of drug particles from adhesive mixtures is facilitated if the rugosity of the carrier particles is reduced [68]. Limits to numerical values for the rugosity were set based on surface characterisation methods such as air permeametry (Kozeny-Carman) and gas absorption (BET-method) without taking regard of the scale of the surface discontinuities. In later studies, carrier surface morphology was studied more in detail with scanning electron microscopes and image analysis techniques for different marketed lactose products with different surface smoothness [69]. From dispersion experiments with pranlukast hydrate-carrier mixtures with these lactose products, it was concluded that a surface roughness on a scale smaller than the diameter of the adhering drug particles (nano- or microrugosity) has a positive effect on the drug fraction released from the carrier surface, whereas surface pores, clefts and discontinuities larger than the drug particles (macrorugosity) have a negative effect. This was explained by reduced contact area and increased distance between the drug and carrier particle for carrier surfaces exhibiting nanorugosity, which reduces the magnitude of the van der Waals force. For the large scale discontinuities mechanical interlocking was proposed as mechanism for increasing the drug-to-carrier bond. It is difficult to draw conclusions from such studies however, as differences in surface structure are linked to differences in polymorphic form. For carrier surface discontinuities much larger than the drug particles also a reduced efficacy of drug aerosolisation (drag and lift type of removal) forces has been mentioned [70], although this may depend on the carrier particle size [71]. Large carrier pores and clefts are furthermore places where multiple contact points between drug and carrier may occur and where impurity concentrations from the mother liquor are highest as such pores are filled with liquid when lactose crystals are taken from the crystallisation tank (Fig. 1A) [40]. In conclusion, the effect of the variable carrier surface rugosity on the fine particle fraction obtained seems to depend on the size of the surface irregularities relative to the size of the drug particles.

4.3. Interacting effects

Referring to the final conclusion in the previous chapter 4.2, the general idea exist that carrier surface discontinuities on a scale larger than the diameter of the adhering drug particles are not beneficial for drug redispersion during inhalation. This idea has been

supported by a series of different studies making use of marketed inhalers like the Diskhaler [32], Spinhaler [72,73], Rotahaler [29,33,74] and Pulvinal [75]. Different carrier rugosities for comparative evaluation were either obtained by selection or by carrier surface modification using techniques like recrystallisation from carbopol, ethanol treatment or special particle smoothing processes in high-speed mixers. Only one example is known in which the benefit of a high rugosity (of roller dried anhydrous beta-lactose) has been mentioned [76]. In this patent the use of the Miat inhaler is described. This type of inhaler has a different dispersion principle than classic capsule (Spinhaler, Rotahaler, Cyclohaler) or blister (Diskus) inhalers: it consists of a helical element in the mouthpiece. This element causes impaction of the particles passing through this mouthpiece. More recently, data have been presented that support this claim and give reason to believe that carriers with large surface cavities can be beneficial indeed when inhalers are used that generate inertial separation forces [77]. For this study a classifier based test inhaler was used which retains the carrier crystals during the dispersion test. The degree of drug particle detachment from the carrier surface was determined by chemical analysis of the residual amount of drug on retained carrier crystals after the test (referred to as carrier residue: CR). **Figure 4** shows the carrier residues for four different granular carriers with large surface cavities and one crystalline carrier with much smaller surface irregularities in the same size fraction 250-355 μm as function of the carrier payload with micronised budesonide at 30 L/min from the test inhaler. The granular carriers were prepared from crystalline products with decreasing median particle diameters with the ranking 100M, 325M, 200M and 450M. **Figure 4** shows that the benefit of a granular carrier structure is first obtained at a carrier payload of 0.4% and higher. The explanation of this figure may be complex. It is likely that at low carrier payload ($< 0.1\%$ drug) a large portion of the drug particles in the mixture is either attached to strong bonding carrier sites or to sites where removal forces are relatively ineffective. Such sites are predominantly within the carrier surface irregularities inside which drug particles are wiped together during the mixing process. When the carrier payload is increased, the number of drug particles relative to the storage capacity of the carrier irregularities is increased, and more particles are attached to weaker binding sites or sites where removal forces are more effective. In addition, the drug particle concentration on the carrier surface is increased and this increases the potential for drug particle agglomeration. Consequently, drug particles can be detached more easily during the dispersion test and the carrier residue decreases. This is

more or less the same for all carrier types. When the carrier payload reaches values at which the surface depressions become saturated with drug, more drug particles become attached to places where they are in reach of the inertial and frictional mixing forces. This, as has been explained in par. 2.3, increases the interparticulate forces in the mixture. It occurs at approx. 0.4% payload for the crystalline carrier and first at much higher payloads for the granular carriers which have larger surface pores and thus, a larger storage volume for the drug. Whether an advantage can be obtained from this sheltering of drug particles from the mixing forces depends on the type of dispersion forces used to detach drug particles during inhalation however.

Another widely accepted starting point for adhesive mixture preparation for inhalation is the assumption that carrier particles should be relatively fine [78] or at least contain a certain mass percent of fines [62]. Whether this increases the fine particle fraction or not may also depend on the type of inhaler used however. This is shown in Fig. 5 for a large number of marketed lactose carrier products in mixtures with 2% budesonide. All mixtures were tested in the Novolizer (Meda) and Diskus (GSK) with different dispersion principles at 4 kPa and the fine particle fractions ($<5\text{ }\mu\text{m}$) as percent of the real dose (from the msli) are plotted as function of the median carrier diameter (Fig. 5A) and percent of lactose fines $<15\text{ }\mu\text{m}$ in the carrier product respectively (Fig. 5B). The marketed lactose products used for these experiments were Respitose SV007, ML001, ML001A, GR001 (from DMV Fonterra Excipients), Lactohale 100, 200 (from Borculo), Inhalac 70, 250 (from Meggle), MM50, 250 (from Epikure). The Diskus, which uses drag and lift forces for dispersion, performs as expected on the basis of the general conception that fine carriers are better. Fine particle fraction $<5\text{ }\mu\text{m}$ increases as function of both the median carrier diameter and the percent of carrier fines. The Novolizer however, shows an opposite behaviour. This has two main reasons. Firstly, the Novolizer has a much more effective dispersion principle based on inertial separation forces, which also remove drug particles from carrier surface irregularities. Secondly, circulation (and retention) of carrier particles in the classifier is improved with increasing diameter. Both examples show that effect of a single variable from the scheme in Fig. 3 may depend on the choice made for any of the other variables which confirms the occurrence of interactions.

5. Taking a critical view

5.1. on the role of carrier surface properties

It is widely believed now that drug-to-carrier interaction is dominated by surface energetics and the existence of sites with higher bonding energy. The Figs. 2 and 4 seem to confirm that active sites exist and that most drug particles are difficult to detach when the carrier surface is loaded with only small amounts of drug particles. This suggests that higher carrier payloads are preferable as they leave an excess of drug particles to be attached to weaker bonding sites. Figure 6 shows for two different carrier payloads with salbutamol sulphate (0.4 and 4%) how the carrier residue decreases with increasing flow rate through a classifier based test inhaler. Such a test inhaler is extremely effective in removing drug particles from the entire carrier surface, including carrier surface discontinuities. Hence, CR continues to decrease with increasing flow rate until a threshold flow rate is achieved above which %CR remains more or less constant. For the 4% mixture in Fig. 6 this is for approx. 0.8% percent CR and for the 0.4% mixture this is for 6.5% CR. Apparently above the corresponding threshold values for the flow rate of approx. 50 to 70 L/min residual drug particles are so firmly attached that they can not be removed. It seems plausible to believe that these drug particles are indeed attached to the strongest bonding sites, which would be the so-called 'active sites'. Therefore, the carrier residue at 60 L/min (or higher) through a classifier based test inhaler could be used as a measure for the degree of occupation of the strongest carrier bonding sites (as function of the mixing time, see par. 2.3) or even the total bonding capacity of these sites (after infinite mixing time). In Table 1 the carrier residue values (after dispersion at 60 L/min) for mixtures with 0.4% and 4% budesonide (on a coarse carrier fraction 250-315 μ) as function of the mixing time (Figs 2B and C) have been expressed as residual amounts (mg) of drug per square meter carrier surface area. For comparison: 5 min for the 4% mixture results in the same residual mg drug per square meter of carrier surface area as 30 min for the 0.4% mixture.

The data shown the Figs. 2, 4 and 6 and Table 1 could have the major implication that the most strongly binding sites (active sites) may not be as important as they have always been regarded. Only a fraction of the dose is attached to these sites as defined above and liberation of drug particles from such sites becomes first of interest at very high dispersion energies. Figure 6 shows that the flow rates through the classifier based test inhaler above which no further drug particle detachment takes place (50-70 L/min) correspond with pressure drops of respectively 8 and 16 kPa. This is far beyond the range of attained

pressure drops through marketed inhalers in daily practice. Because these marketed inhalers are also less efficient in dispersion, the situation at which drug particles have to be detached from these most active sites is unlikely to ever be achieved with these devices. This makes the relevance of the so-called ‘active sites’ in drug-to-carrier interactions questionable when inhalers with low dispersion efficacy are used, but this does not imply that carrier surface properties are irrelevant. The carrier residue decreases over a wide range of flow rates, corresponding with a wide range of separation forces (Fig. 6) which implies that a wide distribution of adhesion forces has to be overcome. Although this seems to be primarily a consequence of the distribution in the particle size of the drug [79], it is partially also the result of drug (re-) agglomeration on the carrier surface, the effect exerted by the inertial and frictional mixing forces on the interparticulate forces in the blend, the variation in carrier binding sites and the difference between cohesive and adhesive forces in the mixture. The contribution of most active binding sites to all these influences may be relatively small.

More recently, active sites are expressed in terms of surface free energy. As discussed in par. 2.2, values presented for the surface free energy of different types of lactose obtained with IGC-measurement typically range from 40 to 50 mJ/m² [41,48,49]. This equals 40 to 50 x 10⁻⁹ μJ per square micron which is approximately the order of magnitude for the contact area of a single drug particle. If this surface free energy is relevant to the interaction forces between the carrier surface and drug particles, there must be a relation with the separation forces needed to dislodge a drug particle from the carrier surface. Such separation forces have been measured with atomic force microscopy (AFM) and they have the order of magnitude of 1 to 1000 μJ for a single drug particle in the micron range (depending on the relative humidity) [39]. So, presented orders of magnitude for the surface free energy and the separation energy differ by a factor 10⁻⁵ to 10⁻⁸. Therefore, it may be questioned whether differences in drug-to-carrier interaction forces can be predictive for differences in surface energy for the carrier fraction. It has been proposed that surface energy in itself is not the parameter to consider. Surface energy should rather be used as an indicator of other variability, like impurity, chemical heterogeneity profile or surface disorder content at the nanometer level (including amorphicity, nano-crystallinity, polymorphism, etc.) [42]. This is an interesting approach. However, if relevant differences in fine particle fractions between different carrier formulations are obtained, which are

likely the effect of carrier surface (and not of mixing) variability, than fine particle fraction itself is the best indicator. Particularly when it is taken into account that surface energy is not a property that varies considerably from one batch of material to the next [42]. And either way, the relation to carrier surface parameters remains to be investigated. Interpretation of surface energy data may be complex as the effects obtained may depend on testing conditions. An example is given in Fig. 7A showing the carrier residue as function of the flow rate for 0.4% budesonide mixtures and a coarse carrier fraction of 250-315 μm . Different mixtures were prepared with different amounts of lactose fines having the same particle size distribution as the drug. The lactose fines have a higher surface free energy ($\gamma_{301\text{-K}} = 44.9 \text{ mJ/m}^2$) than the coarse carrier particles ($\gamma_{301\text{-K}} = 38.2 \text{ mJ/m}^2$) which could be the result of a reduction in the degree of structural order during the micronisation process. When the carrier residues for the drug particles of these mixtures are plotted as function of the surface energy of the carrier blends (Fig. 7B), fine linear correlations are obtained for all flow rates. However, the slopes of the linear curves change from positive at 20 and 30 L/min to negative at 40 and 50 L/min and this suggests that other parameters or effects must be involved

5.2. on the role of amorphous spots

Milling of particles causes local distortion of the lattice structure of crystalline materials. The distortions are referred to as amorphous spots and it has been shown that the presence of such amorphous spots from milling increases the surface energy [50]. On the basis of this increase in surface energy the expectation of an increased interaction force with adhering drug particles seems justified. Therefore, amorphous spots are considered as active sites [80] and effort is put in techniques to quantify small amounts of amorphous material in crystalline carriers [81-84]. It is very difficult to assess the precise effect of the presence of amorphous carrier spots on the drug-to carrier interaction however, as in comparative evaluation studies with purely crystalline carriers other variables are mostly involved too. They include for instance the particle size distribution, which also affects the carrier payload, and the carrier surface rugosity. Therefore, it is almost impossible to quantify the contribution of amorphous carrier fractions to the overall effect, unless the effect of the other variables can be eliminated. For instance Kawashima et al. (1998) used spray dried (amorphous) particles from lactose solution and compared dispersion performance from the Spinhaler before and after re-crystallisation for mixtures with

pranlukast hydrate [69]. They concluded that the moderate fine particle fractions obtained from the mixture with pure amorphous carrier is the result of enhanced van der Waals attractive force due to a larger contact area with the very smooth carrier surface as well as a higher surface energy. After re-crystallisation and sieving to the same size fraction of the amorphous particles, a so-called nanometered carrier particle topography was obtained. Mixtures with these re-crystallised particles yielded a much higher fine particle fraction but this was primarily attributed to a reduced contact area with the drug particles. An interesting comparison for the effect of amorphisation on dispersibility can be made with spray dried drugs. Various studies have shown that highly amorphous spray dried particles can be dispersed either as such or from carrier based mixtures as effectively as micronised drugs, or even better, e.g. [85] for disodium cromoglycate, [86] for ciprofloxacin and doxycycline and [87] for cetorelix acetate. This suggests that the anomeric composition does not have a dominating effect. This may also be concluded from Fig. 8. In this figure, CR (from a classifier based test inhaler) is plotted as function of the flow rate for mixtures with 4% budesonide on a coarse carrier fraction (250-315 μm) with and without 4% lactose fines (LF) having the same size distribution as the drug particles. Two different samples of LF particles were used, one with and one without 30% amorphous material respectively. The addition of 4% LF increases the CR particularly at low flow rates but the increase appears to be rather independent of the presence of amorphous material in the LF particles. Re-crystallisation of the amorphous fraction in the LF particles before the blend with drug and coarse carrier particles is made does not seem to have a significant effect either. Only when the fraction amorphous material is re-crystallised in the mixture a significantly higher CR is obtained. This seems to indicate that the presence of amorphous material is not so much relevant to the magnitude of the adhesive forces between the particles as it is to the stability of the blend. When re-crystallisation occurs in the mixture, capillary and solid bridges may be formed due to the release of excess water when particles undergo the transition from the amorphous to the crystalline state.

5.3. on the role of fines

In their review, Jones and Price concluded that there exist two major mechanisms for the role of excipient fines: occupation of active carrier sites and co-agglomeration with the drug particles [63]. These mechanisms are based on the assumption that fines act either in

competition, or in collaboration with drug particles. This is an incomplete picture however. Fines can also act as carrier particles or as a ternary component, for instance depending on their size distribution relative to that of the drug particles. As an example: a spherical excipient particle with a diameter of 7.5 micron can carry a monolayer of seventy drug particles with 2 micron diameter on its surface in the most open (cubic) arrangement of these drug particles. Due to their high specific surface area, a few percent (by weight) of such fines in a coarse carrier mixture is capable of reducing the payload of the coarser particles considerably. And this may have dramatic consequences for the percent of drug particles released from these coarse carrier particles, as shown in the [Figs. 2A and 4](#). Fines acting as carrier also change the average carrier properties. When the excipient fines are only slightly coarser than the drug particles, they may also act as a buffer taking the shock when the much coarser carrier particles collide with each other during mixing. In this role, fines act as a ternary mixture component. They eliminate largely the effect of inertial and frictional forces during the mixing process. As a result, drug agglomerate break-up, re-agglomeration and migration from weaker to stronger binding sites may be altered and an increase in the interparticulate forces may not occur. The possible effect of all that is shown in [Fig. 9](#). In this figure the carrier residue as function of the flow rate through a classifier based test inhaler is shown for four different mixtures with budesonide. Two of the mixtures contain budesonide only (0.4 and 4% respectively); two mixtures with 0.4% budesonide contain also either 4% lactose fines (LF) having exactly the same size distribution of the drug ($X_{50} = 1.5$ micron) or 4% lactose fines (CLF) having slightly larger median diameter than the drug particles (3.8 micron). Adding 4% LF results in an increase in CR or flow rates up to 35 L/min which can not be attributed to a higher carrier payload alone, because CR of the 4% budesonide mixture takes an intermediate position between CR's for the 0.4% budesonide mixture and 0.4% budesonide plus 4% LF mixture. Adding 4% CLF causes a substantial decrease in CR compared to the 0.4% budesonide mixture alone and this could be the result of reducing the efficacy of the inertial and frictional mixing forces. Mixtures with a higher drug concentration (4% budesonide) and 4% LF or CLF respectively show the same behaviour. Interestingly, carrier mixtures with 4% slightly coarser excipient particles in this study had a higher dispersive surface free energy (43.7 mJ/m^2 at 301 °K) than the mixtures with excipient particles having the same size distribution as the drug (41.9 mJ/m^2 and 301 °K). Compared to the coarse carrier particles alone (38.2 mJ/m^2) these are such marginally differences however, that it is very unlikely

that they can have caused the huge differences in CR in Fig. 9. Between mixtures with LF and CLF particles, both present in an amount of 4% and both increasing the surface energetics to approximately the same extent, the difference in CR at intermediate flow rates (20-40 L/min) is extreme. Therefore, other mechanisms (as explained for the CLF particles) must have dominated the mixture performances.

6. The relevance of inhaler design

So far, most of the energy to improve dry powder inhalation therapy has been focussed on controlling the interparticulate forces in the mixture and little has been undertaken to improve dispersion. Even for many new products in development old capsule based inhalers will be used, like the T- 326 dpi, which is basically the Turbospin of PH&T, for tobramycin inhalation powder (TIP, Novartis) and the Breezhaler, which is a modification of the ISF inhaler for indacaterol (Onbrez, Novartis). Also Forest Laboratories and Bayer Schering Pharma AG make use of the T-326 DPI for their new products Colobreathe and Ciprofloxacin PulmoSphere Inhalation Powder (CPIP).

A major challenge is to find the optimal balance between the three types of forces that govern the particle deposition from dry powder inhaler (dpi) systems: the interparticulate forces in the mixture, the dispersion forces generated by the inhaler device during inhalation and the deposition forces for the aerosol particles in the respiratory airways as shown in Fig. 10. Generating high flow rates through a dpi could increase the dispersion forces, but this also changes the deposition in the respiratory tract. The ideal dry powder inhaler allows the patient to generate only one particular air flow rate through the device which preferably has the order of magnitude of 30 L/min. The ideal dpi also delivers a high and consistent fine particle dose at this flow rate with a mass median aerodynamic diameter (mmad) for the fine particle dose that has been optimised for the target area. On the basis of deposition studies with monodisperse particles it can be concluded that the optimal mmad is larger than 3 μm for upper tract deposition and smaller than 3 μm for central and peripheral deposition at a moderate flow rate of 30 L/min [88]. Active inhalers which use auxiliary energy have been developed to control powder dispersion, like the Dura and Exubera inhalers [89,90], but they have not made it to the market or were withdrawn from it amongst other reasons because they are complex, expensive and vulnerable. A flow manoeuvre independent dispersion is only desirable however, when also the flow rate can be kept constant. Limiting the flow rate to one particular value or

even controlling the flow rate within a narrow range through passive dpi's is quite impossible, as patients operate their devices with variable inspiratory effort. Valve systems opening first at a particular pressure drop across the inhaler and throttling down above a certain upper limit for the flow rate could be developed [Ref. 91 from Kim], but they still leave room for variation and may be highly unpleasant for the patient. Therefore, one of the most successful approaches to obtain a certain control over lung deposition is to increase the inhaler resistance, which make the generation of high flow rates impossible. High resistance passages for the particle laden air stream also facilitate the transformation of the flow effectively into velocity and kinetic energy. This makes high resistance inhalers generally more effective in powder dispersion than low resistance devices. Therefore, inhalers must be designed in such a way that they do not need a high flow rate to generate a high fine particle dose. Due to the effective utilisation of the available energy within the air stream, high resistance inhalers mostly produce an increasing fine particle fraction with increasing flow rate [92]. Unlike what is often believed, this is helpful for obtaining a patient independent therapy. This can be explained by the shift in deposition towards larger airways for particles of the same aerodynamic diameter when the flow rate is increased. Both deposition modelling [93] and in vivo deposition studies [88] give theoretical and experimental proof for this shift in deposition which can be counterbalanced by a higher fine particle fraction as well as a smaller mmad for this fraction at higher flow rates. For the Novolizer (MEDA) with air classifier technology for dispersion, this principle of counterbalancing has been proved with an in vivo deposition study using radiolabelled budesonide [94]. Due to a fine particle fraction which increases from approx. 20% of the real dose at 45 L/min to 30% at 60 L/min and 45% at 90 L/min, the peripheral lung deposition remains fairly constant (6.5% to 7.8% and 8.5% at 45, 60 and 90 L/min respectively) and so does the peripheral/central zone ratio (1.0 to 1.0 and 0.9).

Air classifier technology is one of the dispersion principles that makes use of inertial separation forces. These forces are proportional to the third power of the adhering drug particle diameter. By definition they are higher than drag and lift forces, whereas inertial forces are more effective in removing drug particles from carrier surface cavities too. Besides, in a classifier such inertial forces are sustained over a much longer period than the drag and lift forces in turbulent shear inhalers. Consequently, a more effective dispersion

may be expected. Multiple classifier technology is applied on a new disposable inhaler (Twincer) for extremely high drug doses as in cystic fibrosis and tuberculosis therapy with antibiotics [92]. For such inhalers, optimising the inhaler resistance, the flow break-down and particle circulation in the classifiers is extremely important. For an adequate design of such dpi's the assistance from techniques such as computational fluid dynamics (CFD) and particle tracking (PT) is indispensable.

There are currently few studies in the open literature optimising powder inhaler performance using CFD [95,96]. Recently, CFD has been used to model the air flow in inhaler devices to enhance the understanding of the factors (such as turbulence and impaction) affecting the performance of dry powder inhalers. Coates *et al.* [97-101] have developed CFD models to simulate and examine the flowfield generated in the commercially available Aerolizer[®]. The computational models developed were used in conjunction with experimental aerosol characterisation techniques to create a generic tool to study powder deagglomeration. Through the correct application of this tool, significant information has been gained on the factors affecting agglomerate break-up in dry powder inhalers, with specific focus on the effects of device design and operating conditions. Although the works by Coates *et al* involved only dispersion of powder agglomerates of mannitol particles, the general findings regarding the device design and dispersion mechanisms are largely applicable to the blend systems using lactose carriers.

The nature of the air flowfield generated within the inhaler was simulated by solving the Reynolds Averaged Navier Stokes (RANS) equations together with the SST (Shear Stress Transport) turbulence model [102] and automatic wall functions using the commercial CFD code ANSYS CFX (www.ansys.com/cfx), as previously described [97]. Solving the RANS equations in conjunction with a suitable turbulence model is the most appropriate approach to solving turbulent flows in complex geometries (and is generally adopted for practical engineering problems) as it provides a good approximation of the flowfield without the need for excessive computational requirements [102].

In addition to simulating the air flow generated in the inhaler, the CFD models developed were also capable of modelling the flow of single, un-agglomerated particles within the device. Lagrangian particle tracking was performed as a post-processing operation, in

which the fate of a large number of mannitol particles were tracked through the fluid after release from the capsule region and subjected to drag forces and turbulent dispersion. This was modelled using the approach of Gosman and Ioannides [103]. By setting the different walls within the device to have a zero coefficient of restitution, it was possible to determine the frequency, location and speed of all particle collisions with the different walls of the device.

The computational model developed was validated using Laser Doppler Velocimetry (LDV) techniques by measuring axial and tangential velocities a large number of measurement points across the exit of the inhaler mouthpiece, which were then compared directly with the corresponding CFD results. Good agreement was observed between the computational and experimental results over a range of device designs and flow rates, demonstrating that the computational model could accurately simulate the device flowfield [97]. Visual comparison between the CFD and experimental results was achieved using high-speed photography which reveal motion of the drug particles within transparent Aerolizer[®] devices. **Figure 11a** shows the motion the drug particles take when dispersed by the Aerolizer[®]. Comparing this figure with the particle tracks obtained when the computational models were used to simulate the dispersion of 10,000 drug particles (**Fig. 11**) provides additional evidence of good agreement between the experimental and computational results, and shows that the CFD model closely represents the flow of particles within the inhaler.

The design of a dry powder inhaler is vital to control the dispersion of drug agglomerates in the device [104,105]. All passive dry powder inhalers on the market today are designed with three common design features, namely a mouthpiece, air inlets and a powder storage/dispensing system. Additional design features, such as grids and rotating capsules, can also be added to the device to provide further powder deagglomeration. Recent studies using CFD have significantly enhanced the knowledge of how inhaler design contributes to the overall inhaler performance, leading to the following findings.

Effect of Grid Structure. A large number of dry powder inhalers are designed with an inhaler grid, primarily included to prevent the drug filled capsule and capsule pieces after piercing from exiting the device during inhalation. However the inhaler grid is also

included to generate high turbulence levels within the device and to enhance dispersion by inducing powder deagglomeration through powder impaction with the grid structure. Voss and Finlay [106] have shown that turbulence plays a definite, although not necessarily the dominant, role in fine particle dispersion and that mechanical impaction of the powder on a grid is not an effective break-up mechanism. The presence of the grid provides the opportunity for increased or reduced turbulence to affect the inhaler performance.

Coates *et al* [97] found that the structure of the inhaler grid affects the overall performance of the device (FPF_{loaded}), as well as on the amount of powder retained in the inhaler mouthpiece, without significantly changing the inhaler dispersion performance ($FPF_{emitted}$). Examining the flow of particles experienced in the Aerolizer[®] with three different grid structures (as illustrated in Fig. 12A), it was found that the ‘full’ inhaler grid acts to convert the high velocity tangential air flow entering the device into a low velocity, predominantly axial air flow exiting the mouthpiece. As the grid voidage was increased, the air flow became predominantly tangential occurring in the mouthpiece for the ‘grid 2’ case (Fig. 12B), which increased the degree of particle-mouthpiece contact and consequently, the amount of powder retained in the mouthpiece. For the full grid case, 17% of the total amount of powder loaded in the capsule was retained in the mouthpiece after dispersion, which increased to 25 and 34% for the grid 1 and grid 2 cases, respectively. This led to a significant reduction in the FPF_{Loaded} from 47.6 (± 2.2) % for the full grid to 39.2 (± 2.0) and 35.2 (± 1.9) % for the grid 1 and grid 2 cases, reducing the overall performance of the inhaler. Hence, the original Aerolizer[®] grid design performed better than the modified grids with higher voidage.

The structure of the inhaler grid also had a strong effect on the intensity of grid turbulence, with the turbulence intensity generated immediately upstream of the grid reduced as the voidage of the grid was increased (Fig. 12C). In addition, the number percentage of high speed particle-grid impactions was decreased with increasing grid voidage (from 59% for the full-grid to 40 and 20% for the grid 1 and grid 2 cases, respectively). Therefore increasing the voidage of the grid reduced the deagglomeration potential of the flowfield generated in the device, due to lower grid turbulence and fewer particle-grid impactions. However, as the voidage of the grid was increased, the number percentage of drug particle

impactions with the mouthpiece increased (from 22% for the full-grid to 57 and 88% for the grid 1 and grid 2 cases, respectively), improving the deagglomeration potential of the device flowfield. This increased deagglomeration potential was probably balanced out by the reduced deagglomeration potential due to lower grid turbulence and agglomerate-grid impactions, resulting in no significant difference in the inhaler dispersion performance (FPF_{emitted}) observed experimentally.

Effect of Mouthpiece Length. The length of an inhaler mouthpiece controls the level of air flow development through the mouthpiece and the nature of the flowfield exiting the device. Undeveloped flow can contain regions of high velocity that can enhance oropharyngeal impaction upon inhalation. More developed flow through the mouthpiece leads to a more uniform flow profile at the device exit. This uniform profile reduces the regions of high velocity, potentially reducing oropharyngeal deposition and improving the overall inhaler performance. However, for the Aerolizer[®] the length of mouthpiece was found to play only a minor role in the overall inhaler performance. As the length of the mouthpiece was reduced to three-quarters and one-half of the original size, no significant difference was observed in the FPF_{loaded} (45.4 ± 1.6 and 46.3 ± 1.5 %, respectively vs 46.7 ± 2.2 % in the full-length) while the difference in the throat impaction is only minimal (6.7 ± 0.1 and 6.2 ± 1.2 %, respectively vs 4.9 ± 0.5 %). However there was a slight reduction in the amount of powder retained in the device after dispersion as the mouthpiece length was reduced, indicating that a shorter mouthpiece will slightly improve the overall performance of the inhaler by increasing the amount of powder emitted from the device.

Role of the Rotating Capsule. A large number of the dry powder inhalers on the market use a capsule to store and dispense the drug formulation. Upon inhalation, the flowfield generated within these dry powder inhalers acts to rotate and/or vibrate the capsule to eject the powder contained in the capsule through the capsule holes into the surrounding flowfield. It is believed that agglomerates could break-up through a number of capsule induced deagglomeration mechanisms: 1) Powder agglomerates could impact with the internal walls of the capsule, prior to ejection, as it rotates or vibrates; 2) Forcing powder agglomerates through the small capsule holes could cause large agglomerates to break up, preventing slugs of powder from exiting the capsule; 3) High speed impactions with the surrounding walls of the device could occur as the particles are ejected from the capsule,

and 4) The moving capsule could act as a rotor to deagglomerate ejected particles through mechanical impaction. Some of these mechanisms may dominate or interact to affect particle dispersion in the inhaler.

The presence, but not the size, of a capsule was found to have a significant effect on the inhaler performance. No significant difference in the overall inhaler performance was observed as the size of the capsule used to disperse the drug powder (size 3, 4 and 5) was varied. When powder was loaded directly into the device, onto the surface adjacent to the spinning capsule, the presence of the capsule was found to actually reduce the overall turbulence levels generated in the device by more than 65% (Fig. 13), lowering the $\text{FPF}_{\text{loaded}}$ from $40.4 \pm 2.2\%$ without the capsule to $35.5 \pm 2.2\%$ with the capsule present. However, when the powder was loaded inside the capsule, additional ‘initial capsule deagglomeration’ was provided by the capsule (produced by forcing powder through the capsule holes) that could far outweigh the performance reduction due to reduced turbulence levels. The overall performance of the inhaler was increased ($\text{FPF}_{\text{loaded}}$ $46.7 \pm 2.2\%$). The results further showed that capsule-particle impaction is a weak mechanism for deagglomeration. The potential role of the capsule acting as a rotor to cause deagglomeration by mechanical impaction has an insignificant effect on the overall performance of the inhaler.

Influence of Air Flow Rate in the Device. A major potential disadvantage of passive dry powder inhalers is their performance dependence on the patient’s inspiratory air flow. Inspiratory air flow through a dry powder inhaler controls both the turbulence levels generated in the device and the intensity of particle impactions, which are pivotal to the inhaler dispersion performance. Numerous empirical studies have shown that inhaler performance is increased by a higher inspiratory flow rate [105,107,108] due to increased deagglomerating forces generated in the device. Increasing the device air flow rate initially improved the mannitol powder dispersion performance of the Aerolizer[®], but only up to 65 L/min, and further increases in the device flow rate did not lead to improved inhaler dispersion performance. This indicates that the deagglomerating forces required to maximise the dispersion performance of the Aerolizer[®]/mannitol system had been generated in the device at 65 L/min. Coates *et al* [98] hypothesised that critical flow turbulence levels and particle impaction velocities must exist at which the inhaler

dispersion performance is maximised, i.e. beyond these critical levels dispersion would not improve further. However, it was necessary to understand which turbulent mechanisms due to air flow are dominant in determining particle break-up. The turbulence kinetic energy which is a commonly used parameter to assess turbulence intensity, is a measure of the absolute turbulence level generated in the device, whereas the integral scale strain rate (ISSR: defined as the turbulence eddy dissipation rate divided by the turbulence kinetic energy) is a measure of the velocity gradient across the integral scale eddies (the most energetic occurring in a turbulent flow [109] and is hence a more appropriate parameter to study agglomerate break-up. Using CFD models, it was found that an increasing trend in the ISSR was observed with flow rate in Aerolizer[®]. At the critical device flow rate of 65 L/min (where there was no further improvement in the FPF_{loaded} experimentally) a volume averaged ISSR of 5400 s⁻¹ was generated in the inhaler. Further increases in the integral scale strain rate did not improve dispersion. Similarly, at the critical device flow rate, particle impaction with the grid and inhaler base occurred at average velocities of 19.0 and 12.7 m/s, respectively.

This study was performed to quantify integral scale strain rates and particle-device impaction velocities that occurred at a flow rate where the Aerolizer[®] dispersion performance was maximized. However it is unclear whether these are the critical turbulence levels and particle impaction velocities required to maximize the performance of other dry powder inhalers. To test the validity of the findings, the study methodology was applied to the Aerolizer[®] with different air inlet sizes (namely the full air inlet and designs consisting of two-thirds and one-third the original air inlet size (Fig. 14A). Reducing the air inlet size increases the velocity of the entrained air flow, which increases the turbulence levels generated in the device. Therefore at the same device flow rate, a different turbulence distribution is generated in the device for each air inlet size, which can be used to determine the effect of varying turbulence distribution on the inhaler dispersion performance (Fig. 14B). The experimental results showed that at low flow rates (30 and 45 L/min), reducing the air inlet size increased the inhaler dispersion performance by increasing the turbulence levels and particle impaction velocities generated in the device above the critical levels. These results demonstrated that the optimum dispersion performance of a dry powder inhaler can be predicted if details of the device flowfield are known. Reducing the size of the air inlet also reduced the time taken for powder to empty

the device, but increased the time required for flow to be fully-developed within the device. In contrast, at higher device flow rates (60 L/min), reducing the size of the air inlet reduced the inhaler dispersion performance because a large amount of powder was released from the device when both the turbulence levels and particle impaction velocities had not been fully developed. This result highlights the importance of minimising the amount of powder released from the device prior to full flow development. However, the computational model developed was unable to determine which deagglomeration parameter (i.e. integral scale strain rates or particle impaction velocity) had the most significant effect on the inhaler dispersion performance.

Despite the importance of typical levels of turbulence and particle impaction velocities required for optimal inhaler design, no other studies have been reported in the open literature to determine this information for other inhalers. Whilst it is difficult to obtain quantitative measures of these critical conditions, it is possible to determine qualitatively whether they exist. As the above results have demonstrated, computational fluid dynamics is well-suited for solving the air flowfield generated in complex geometries. However, existing CFD models are limited for examination of agglomerate break-up. Discrete element method (DEM) modelling, which uses microscopic force balances to model the forces acting between individual particles in agglomerates, can be used to develop models of agglomerate break-up due to interaction with the turbulent flowfield and impaction with solid walls [110-114]. These models can be coupled with CFD to examine powder deagglomeration on a particle scale. Despite limitations in the number of particles that can be simulated, DEM-CFD models would provide a powerful tool to understand powder deagglomeration mechanisms in dry powder inhalers to optimise DPI designs in the future.

7. Conclusions

In carrier based mixtures for inhalation a proper balance has to be obtained between the stability of the blend during storage and handling, and dispersibility during inhalation. This requires control of the interparticulate forces in the mixture in order to prevent segregation on the one hand and insufficient liberation of drug particles in the required aerodynamic size distribution from the blend on the other. Controlling these forces is impossible without understanding the processes of mixing and dispersion and knowing the variables that

influence the outcome of these processes. It has been shown that the variables that are relevant to these processes may influence each other in different ways and that by changing one variable, the effect of some others may be reversed. This may explain why opposite conclusions have been drawn in literature regarding the effect of a single variable and it is recommended that future research is particularly focussed on the interactions between these variables. The effect of variables may also depend on specific properties of the variable, as has been shown for the role of fines. For some of currently most extensively investigated variables the relevance may be questionable. It can be computed that values presented for the surface energy of carrier particles are of a completely different order of magnitude than the separation energies (for drug particle detachment from carrier particle surface) they are supposed to influence. Because surface energy can be the net effect of various properties like impurity, chemical heterogeneity or surface disorder content, surface energy is rather an indicator than a parameter to be controlled. Finally, the importance of inhaler design appears to be neglected in many studies. By using high efficacy devices, generating the appropriate type of dispersion forces, the influence of many mixture variables can be reduced considerably, making research into these variables less needed.

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Table 1: Budesonide carrier residue values after dispersion at 60 L/min in test inhaler CVI (CR₆₀) and real residual mg drug per square meter carrier, both as function of the mixing time in a Turbula (T2C) tumbling mixer (90 rpm, batch size 25 mg in a 160 cm³ stainless steel mixing container) for two different carrier payloads (0.4% and 4%) on a coarse carrier fraction 250-315 µm.

A. percent CR60					
	2 min	5 min	10 min	30 min	60 min
0.4% mixture	3.5	8.1	13.0	16.8	24.4
4% mixture	0.9	1.7	1.8	3.2	5.2
B. real residual amount (mg) of drug per square meter carrier surface					
0.4% mixture	10.14	23.19	37.68	48.55	71.01
4% mixture	26.09	49.28	52.17	92.75	150.72

Figure 1

A

Carrier size fraction 45-63 μm

Carrier size fraction 150-200 μm

B

Figure 2

Figure 3

Figure 4

Figure 5

A

B

Figure 6

Figure 7

A

B

Figure 8

Figure 9

Figure 10

Figure 11 – to be obtained.

Figure 12

A

B

C

Figure 13

Figure 15

A

B