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Recent Advances in the Fundamental Understanding of Adhesive Mixtures for Inhalation

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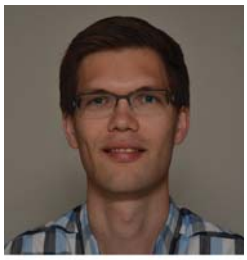

Floris Grasmeijer

Abstract: Adhesive mixtures for inhalation are the most widely used type of formulation in dry powder inhalation products. Although they have been the subject of active research, the relationships between properties of the starting materials, the mixing and dispersion processes, and the dispersion performance of this type of formulation are generally poorly understood. Interactions between relevant variables have been mentioned as an important cause. By reviewing the effects on mixture dispersion performance of the most widely studied formulation variables we try to find out whether or not the understanding of adhesive mixtures has improved in recent years. We furthermore propose an approach that may potentially accelerate the process of understanding. General conclusions concerning the effects of the variables considered cannot be drawn, because inconsistent findings are reported throughout the literature for all of them. These inconsistencies are indeed largely the result of interactions between variables of the formulation and dispersion processes. Mechanisms for most of the observed effects and interactions have been proposed, but they often remain unproven and, therefore, speculative. We have attempted to condense the knowledge from the literature into a theoretical framework that is intended to help explain the interplay between variables. According to this framework, only few mixture properties are key to understanding the effects of and interactions between formulation variables. Therefore, we suggest that the development or optimisation of techniques to accurately characterise these mixture properties could be an effective approach to further the fundamental understanding of adhesive mixtures for inhalation and enable their rational engineering.

Keywords: Carrier particle size distribution, carrier surface roughness, cohesion-adhesion balance, drug content, fines, interactive mixtures, ordered mixtures, powder dispersion.

INTRODUCTION

Research into adhesive mixtures for dry powder inhalation has been blooming especially over the past two decades. Since the introduction of the 'ordered mixing' concept by Hersey in 1975 [1] many studies have focussed on controlling the adhesion forces between fine, micrometre sized drug particles and coarse excipient particles. Initially such studies were performed from a tabletting perspective, in which maximising mixture homogeneity and stability are the key objectives. With the application of adhesive mixing to powder formulation for pulmonary drug delivery, mixture dispersibility became a primary endpoint as well [2]. A non-exhaustive review of 111 research articles, in which the adhesion force between drug and carrier particles or dispersibility of adhesive mixtures from a dry powder inhaler are primary endpoints, learns that this research area has received attention especially from the late nineteen-nineties onwards (Fig. **1**). Formulation variables that have been studied in an attempt to optimise the stability or dispersion performance during inhalation of adhesive mixtures most often concern properties of the carrier excipient, such as its particle size distribution (PSD) or its surface roughness (Fig. **2A**). Alpha-lactose monohydrate is the excipient material most commonly used in adhesive mixtures for inhalation, but other types of carrier material have also been studied. For this, over the years increasingly advanced powder and particle characterisation techniques have been applied, often in combination. Frequently used techniques include for instance scanning electron microscopy (SEM), atomic force microscopy (AFM), and X-ray powder diffraction (XRPD), as is shown in Fig. **2B**. An excellent discussion on the use of these techniques for the characterisation of components in dry powder inhalation products has been published previously [3].

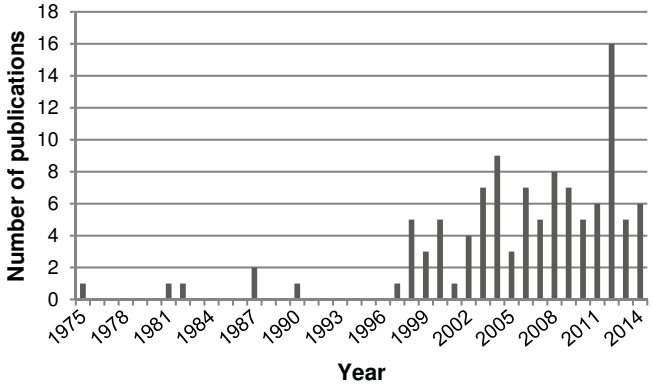

Fig. (1). Approximate number of publications on adhesive mixtures by year. References included: [5, 8-29, 31-35, 38-42, 44-49, 51-53, 55-84, 86-89, 91-95, 97-99, 102, 104, 109-133].

Despite the vast body of scientific literature on adhesive mixtures for inhalation and the advanced characterisation techniques applied, the general consensus seems to be that relationships between properties of the starting materials, the mixing process, the dispersion process and mixture dispersion performance are not well understood [4]. Interactions between variables that are relevant to the dispersion performance of adhesive mixtures greatly complicate this understanding and have, therefore, been mentioned as a major cause [2, 5]. As a result, the development of adhesive mixtures for dry powder inhalation products is mostly an empirical endeavour, which does not comply with the 'enhanced quality by design approach' to product development as advocated by the United States Food and Drug Administration [6].

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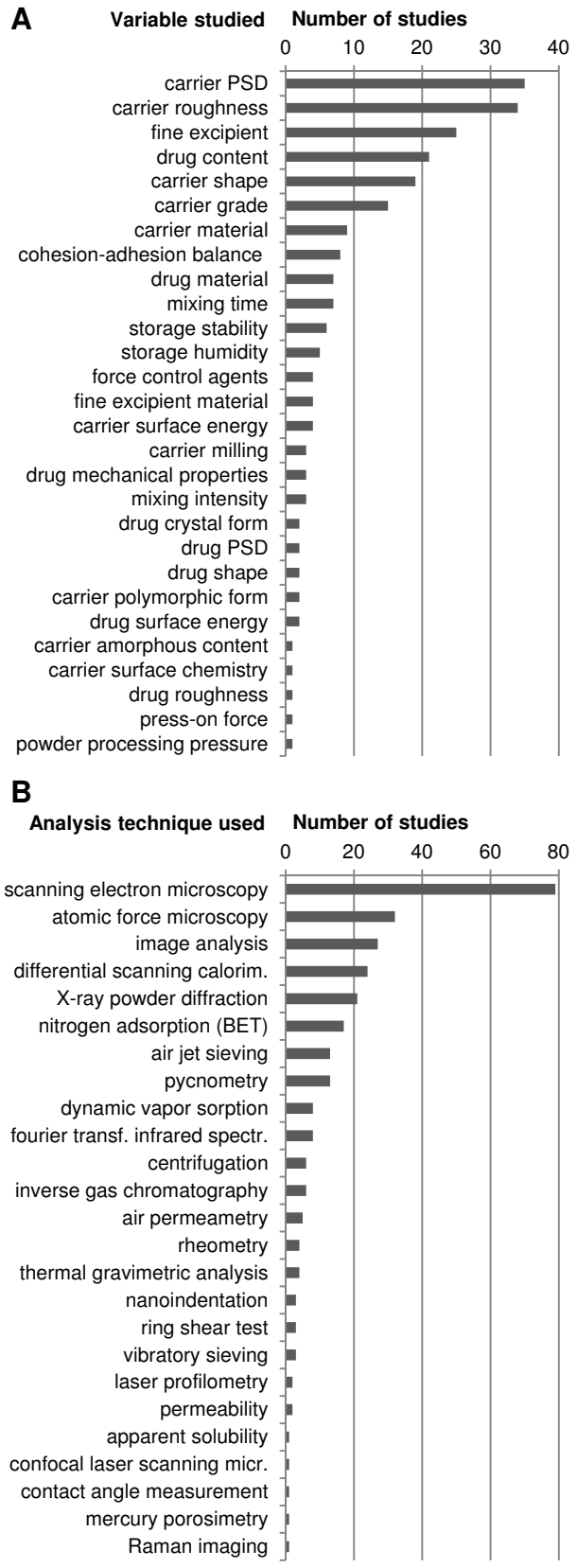

Fig. (2). Characteristics of the reviewed literature on adhesive mixtures for inhalation. A: frequency by which different formulation variables were studied; **B:** frequency of use of different analysis techniques. References included in the characteristics: [5, 8-29, 31-35, 38-42, 44-49, 51-53, 55-84, 86-89, 91-95, 97-99, 102, 104, 109-133].

The apparent discrepancy between research effort put forward and fundamental understanding obtained concerning adhesive mixtures for inhalation is central to this review. For the most widely studied formulation variables (Fig. **2A**) we will attempt to provide a clear overview of the literature regarding their effect on dispersion performance. Furthermore, given the wealth of data available we will discuss whether the general consensus that adhesive mixtures for inhalation are not fundamentally understood is indeed justified and, if so, in which directions the solution to this challenge may be found. Please note that for pragmatic reasons not all aspects concerning adhesive mixtures are discussed in this review. The scope of this review is dictated mostly by the frequency by which certain aspects have been studied, and not by their perceived relevance. Examples of important aspects that have, nonetheless, been omitted from this review are the effects of formulation variables on mixture homogeneity and storage stability and the surface modification of particle surfaces using additives such as magnesium stearate. An in depth review on the latter subject was recently written by Zhou and Morton [7].

THE EFFECT OF CARRIER PARTICLE SIZE DISTRIBUTION

The term 'carrier particle size distribution' may not be the most unambiguous term to use when referring to the particle size distribution of the major excipient material in adhesive mixtures for inhalation. After all, at what size does an excipient particle still act as a carrier when one or more drug particles adhere to it? Even the coarsest excipient material will contain particles as fine as the drug component due to abrasion during the manufacturing process, during blending, or both. And although these fine excipient particles may not strictly act as 'carrier particles', they can greatly affect a blend's dispersion performance, even if they amount up to only a fraction of the total excipient mass. In fact, many studies conclude that the effect on dispersion performance of differences in the particle size distribution between lactose grades, sieve fractions or 'artificial blends' is predominantly related to the mass fraction of fine particles [8-16]. For example, Islam *et al.* found that an inverse linear relationship between the median particle size of different lactose sieve fractions and the fine particle fraction (FPF) of salmeterol xinafoate disappeared after decantation of fine lactose material in absolute ethanol [12]. The inverse relationship could be restored by adding fine lactose particles (< 5 μm) to the decanted fractions, even though the decantation process had also caused a change in the surface roughness of the coarse carrier particles. In other words, in contrast to the fine lactose content, the size distribution of the coarse carrier particles (ranging from 45-63 to < 106 μm) did not seem to affect mixture dispersion performance and the presence of fines had a dominant effect on dispersion performance over carrier surface roughness in this particular study. Therefore, in discussing the effects of carrier particle size distribution on dispersion performance, a clear distinction has to be made between the effects of coarse and fine excipient particles.

Coarse Excipient Particles

The aforementioned example may give the impression that the relevance of the size distribution of the coarse carrier fraction is strictly related to factors other than dispersion performance, such as mixture flowability. Although this is far from true, the influence of coarse carrier size on mixture dispersion performance is not consistent throughout the literature. Some studies found little to no effect of coarse carrier size on mixture dispersion performance [9, 10, 12, 17-20], whereas trends of increasing [21-23] and decreasing [17, 21, 22, 24-29] dispersion performance with an increase in coarse carrier size have also been reported. These discrepancies clearly show that other, interacting factors must be in play.

Donovan and Smyth showed that one such interacting factor is the surface roughness of the carrier particles [21]. They used crys-

talline or granulated lactose carrier material to prepare a series of narrow size fractions, increasing in diameter from < 32 μm to 250-300 μm. Dispersion of 2% budesonide blends with the Cyclohaler at 60 L/min resulted in a trend of decreasing fine particle fraction from 18% to 8% of the total dose with increasing crystalline carrier size, whereas the granular carrier resulted in a trend of increasing fine particle fraction between 8% and 17% of the total dose. In a follow-up study the same group showed that also the type of inhaler used can be of influence [22]. The trend of improved dispersion performance with increasing granular carrier size was more pronounced for the Cyclohaler than it was for the Handihaler. They showed with computational fluid dynamics simulations that an increase in carrier size resulted in a larger increase in the number of collisions of the carrier particles with the inhaler wall for the Cyclohaler. Hence, a difference in the contribution of inertial separation forces from particle collisions to the detachment of drug particles from the carrier particles may have caused the observed difference between the inhaler devices. The interaction between coarse carrier size and inhaler type was also demonstrated by Hagedoorn *et al.* [30]. At increasing median carrier diameter they obtained a higher FPF from the Novolizer, whereas that from the Diskus became lower. These devices contain distinctly different dispersion principles, generating primarily inertial or aerodynamic separation forces, respectively.

Besides interacting parameters, the number of factors directly linked to carrier particle size and the different effects they can have further complicate the unravelling of the exact mechanisms by which carrier size affects dispersion performance. For example, de Boer *et al.* showed that carrier surface roughness and the amount of impurities (e.g. protein residues) per unit carrier surface area increase with the size of lactose carrier particles [17]. It was suggested that these changes result in higher adhesion forces between drug and carrier particles, because they result in a higher number of contact points or a larger contact surface area per contact point, respectively. It was furthermore suggested that the higher mass of larger carrier particles and their better flowability could result in higher frictional and compressive forces during mixing, thereby contributing to increased drug-carrier adhesion forces. At the same time, larger carrier surface irregularities can offer protection to drug particles from compressive forces during mixing or from aerodynamic detachment forces during dispersion. They may furthermore increase drug agglomeration, which can improve drug detachment due to the more favourable ratio of separation to adhesion forces for larger particles but does not necessarily result in higher fine particle fractions if the agglomerates are not further broken up during dispersion [25, 31-33]. An increase in carrier particle size reduces the specific carrier surface area and leads to higher drug carrier surface payloads (in mg/m^2) at the same drug content. Similar effects to those from an increase in drug content, as will be discussed further on, may therefore be expected. It was also suggested in several studies that the higher mass of larger carrier particles may improve dispersion due to 'increased momentum transfer' upon collision with the inhaler wall or other carrier particles [21, 22, 26, 29]. However, inertial separation forces depend on the mass of the drug particles and the deceleration of the carrier during a collision, rather than carrier mass. Furthermore, a dominant role of carrier-carrier collisions is questionable in this respect, since all particles likely move roughly in the same direction with a similar velocity in a relatively dilute system.

In an attempt to eliminate as many of the linked parameters as possible, Ooi *et al.* performed a study using perfectly smooth polystyrene beads of different sizes as carrier material [26]. An increase in median carrier diameter from 82 to 582 μm resulted in a decrease in FPF from 23-25% to 6-18% of the emitted salbutamol sulphate dose at different flow rates. Similar trends were observed at different drug contents in a later study from the same group [29]. The authors attributed this effect to a reduction in carrier-carrier collisions during dispersion. However, evidence to corroborate such an explanation was not provided. The possibility of an increase in press-on forces during mixing for larger (heavier) carrier particles causing higher drug carrier adhesion was considered by the authors, but deemed unlikely as glass beads (with a higher density) instead of polystyrene beads resulted in a similar dispersion performance. Unfortunately the difference in surface chemistry between the polystyrene and glass beads forms a confounding variable, and such an experiment can, therefore, not be considered irrefutable. The results obtained with polystyrene beads are not in agreement with the results obtained by Tuli *et al.*, who also used relatively smooth spherical carrier particles, only now consisting of polycaprolactone coated with magnesium stearate or leucine [23]. For increasing median carrier diameter from 28 to 150 μm dispersion performance increased from 2.9-5.3% to 13.1-20.4%. With SEM the authors observed increased agglomeration of the drug on larger carrier particles. This may contribute to the reported effect as an increase in drug particle size increases the separation forces during dispersion more so than the adhesion forces and, therefore, improves particle detachment from the carrier [34-36]. Perhaps the coating of the carrier with magnesium stearate or leucine caused this agglomeration behaviour by shifting the balance between adhesive and cohesive forces in the direction of the latter. A noteworthy difference that could further have caused the discrepancy between the studies with polystyrene and polycaprolactone beads besides the carrier material is the mixing process. The polystyrene beads were mixed for half an hour with a Turbula blender at 46 rpm, while the polycaprolactone beads were mixed with the drug in a glass vial by shaking it manually for only 5 minutes. The shorter and supposedly milder mixing process may have reduced an influence of carrier size on drug compression to the polycaprolactone surface during mixing. The above goes to show that, even with an 'idealised' carrier material, interacting and possibly linked effects make it impossible to draw general conclusions regarding the effect of coarse carrier size on dispersion performance.

Fine Excipient Particles

The size below which 'coarse' excipient particles become 'fine' cannot be defined very sharply, but it appears that excipient particles are most relevant to dispersion performance roughly below 10 μm. For example, Guenette *et al.* showed that a positive relationship between the fine lactose content of different lactose blends and the fine particle dose of salbutamol sulphate was strongest and constant for cut-off values < 10 μm [16]. If the cut-off value for the fine lactose fraction was increased from < 10 to < 35 μm, the coefficient of determination (R^2) of a linear relationship found between fines content in the mixture and fine particle dose gradually decreased from 0.98 to 0.87. In line with these results, Kinnunen *et al.* found that, for a large dataset obtained with ternary mixtures containing different grades of lactose and types of added fine lactose, a lactose fraction < 4.5 μm was much more important to the FPF of budesonide from dispersion with a Cyclohaler than lactose fractions < 15 and < 30 μm [15]. In studies focusing specifically on the effects of fine excipient particles, median diameters of added fines fractions are commonly between 2-10 μm [37].

The effects of fines have long been consistent throughout the literature, but recent studies have shown that also for this formulation variable interactions with other variables can cause apparently contradictory results. After an extensive review of the literature on this subject in 2006, Jones and Price concluded that the presence of fines in adhesive mixtures is very consistently related to a beneficial effect on dispersion performance [37]. Since then, few studies have shown that the addition of a so-called ternary component can cause a decrease in dispersion performance or hardly any effect as well [38-41]. In one of these studies the addition of fine lactose particles caused a reduction of the drug fraction that detached from the carrier during dispersion from 24.6% to 6% [40]. This effect depended strongly on the inhalation flow rate, the particle size dis-

tribution of the fine excipient and the drug content. A slight decrease in FPF from 15.7% to 14.5% and 15.4% was found by Kinnunen *et al.* for 0.8% budesonide formulations to which 2.5% or 5% milled lactose fines were added, respectively. This decrease in dispersion performance was only observed with the Rotahaler and not with the Handihaler. In another study the fines were added to mixtures with exceptionally low carrier to drug ratios of 1:1 and 4:1 [39], where more common ratios in adhesive mixtures for inhalation are 24:1 or higher (i.e. drug contents < 4% w/w) [42]. Such high payload mixtures deviate from standard adhesive mixtures in the sense that cohesive forces dominate the adhesive forces, and they have been referred to as 'supersaturated ordered mixtures' [43].

In their review, Jones and Price discussed two hypotheses regarding the mechanisms by which fine excipient particles could affect dispersion performance: the 'agglomeration hypothesis' and the 'active sites hypothesis', first proposed by Lucas *et al.* [37, 44]. According to these hypotheses fines improve dispersion performance by forming agglomerates or 'multiplets' with the drug particles that are more easily detached from the carrier surface than the primary particles. Alternatively, fines supposedly occupy so-called 'active sites' or strong binding sites on the carrier surface, leaving only weaker binding sites available for the drug particles [44, 45]. Jones and Price concluded that experimental evidence to support these hypotheses was thin or lacking, and therefore, the mechanisms described remained speculative. In addition, these mechanisms do not explain the few more recent instances in which fines caused a reduction in dispersion performance. However, some new evidence to support mainly the agglomeration hypothesis has been published and several additional hypotheses regarding the working mechanism of fines have been proposed, as will be discussed in the following paragraphs.

Further support for the agglomeration hypothesis has been found in microscopy and SEM images of adhesive mixtures [5, 38, 40, 46]. In addition, it was shown by Jones *et al.* that fines-drug combinations that are more adhesive, and therefore theoretically more prone to agglomeration, resulted in a larger relative improvement of the fine particle dose. They also showed that these combinations resulted in a secondary mode in the particle size distribution of the aerosol cloud at larger particle sizes, which suggested that indeed agglomeration of the fine components occurred [47]. Finally, Kinnunen *et al.* identified composite budesonide-lactose agglomerates on stage 2 of the Next Generation Impactor with a Raman imaging technique after dispersion of a ternary formulation [48]. They argued that such a finding is suggestive of the agglomeration and consequential co-deposition of fines and drug particles. The possibility of composite agglomerates being formed upon deposition of primary particles on stage 2 of the NGI was not discussed, however. In addition, if co-deposition of drug-fine agglomerates plays an important role, one may wonder why an optimal effect seems to be achieved with fines having a median diameter of roughly around 5-8 μm, i.e. slightly larger than most defined fine particle fractions [37, 49].

Although the existence of 'active sites' on lactose carrier surfaces is quite evident, their relevance with respect to the effects of added fine excipient particles on dispersion performance remains questionable to date. As discussed by Jones and Price in their review, most evidence in support of the active sites hypothesis comes from experiments in which the mixing order of the fines and drug component is changed [37, 44]. The results of such mixing order experiments are not consistent throughout the literature, however, and Jones *et al.* showed that this is largely the result of interactions with other variables such as the mixing time and the drug content [5]. In addition, Grasmeijer *et al.* showed that multi-order interactions with inhalation flow rate and the size distribution of the fines can occur as well [40]. In an extensive discussion they furthermore argued that mixing order experiments have often been interpreted based on speculative assumptions, and that a correct interpretation would also depend strongly on how 'active sites' are defined. The activity of carrier surface sites has most often been defined in terms of their binding strength or energy towards contacting drug particles. However, it was recently argued that a broader definition, one which also includes the effects of the carrier surface on separation or dispersion forces, would be more relevant to mixture dispersion performance and, therefore, more useful [50]. Therefore, the relevance of active sites will likely depend on other formulation and dispersion conditions, as well as on how they are defined exactly.

Other mechanisms that have been proposed to explain the effects of fines on dispersion performance may also play a role under certain conditions, but they are not well supported by hard evidence either. Shur *et al.* presented an explanation that was later referred to as the 'fluidisation hypothesis' [51]. They showed with high speed imaging that, by increasing the tensile strength of the bulk powder, fines cause the powder to be entrained more by a fracture mechanism than by gradual erosion. As a result, the powder is likely entrained at higher air velocities and more energy will be available during its dispersion. Furthermore, the authors argued that when the powder is entrained as a dense 'plug', more particle-particle collisions would occur during dispersion, which could contribute to an improvement in dispersion performance. Indeed, increasing fines contents are associated with poorer flow and fluidisation properties of adhesive mixtures, but this does not always correlate well with formulation dispersion performance [41, 52]. According to another hypothesis, fine excipient particles act as a buffer between colliding carrier particles, thereby protecting drug particles that are smaller than the fines from compressive forces during the mixing process [53]. An indication in support of this hypothesis was provided in a study by Grasmeijer *et al.*, who showed that, at certain inhalation flow rates, the addition of fines similar in size to the drug particles (2.0 μm median size in their study) caused less drug to detach from coarse carrier particle during dispersion, whereas fines slightly coarser than the drug (3.9 μm median size) increased the detached drug fraction significantly [40]. However, in a later study it was shown that the fines of similar size to the drug particles resulted in a lower apparent solubility of salmeterol xinafoate after mixing with a coarse carrier than the coarser fine excipient particles [54]. This was considered indicative of lower mechanical stress on the drug particles during mixing and, therefore, presumably of lower press-on forces. As a result, the 'buffer hypothesis' seems to be an unlikely explanation of the difference between the two fines size fractions. A lowering of mechanical stress and compressive forces during mixing may also result from poorer flow properties of the mixture with increasing fines contents, especially in tumbling type mixers. Unfortunately, the apparent solubility data were not related to the flow properties of the powder. In their study with different size fractions for the fines, Grasmeijer *et al.* also proposed that these fines, when small enough, may form coherent fine particle networks from which the drug is difficult to detach [40]. They speculated that coarser fine excipient particles prevent the formation of or (at high drug loads) disrupt such networks, because they result in a lower tensile strength of the fine particle assemblies and are also more susceptible to mixing forces that cause their redistribution over the carrier surface. This 'tensile strength hypothesis' was corroborated only with SEM images. As mentioned, the inhalation flow rate and drug content were identified as an important interacting variable in this study. Furthermore, a very coarse carrier fraction (250-315 μm) was used with large surface irregularities in which the coherent networks formed. Such an effect could be less pronounced for smoother (finer) coarse carrier fractions. Given their study results and the evidence from literature, Grasmeijer *et al.* argued that fine excipient particles can have any effect on dispersion performance and that that they most likely bring about their effect through a combination of all the different mechanisms proposed. The choice for interacting variables, such as the inhalation flow rate, the size distribution of the fines or the drug content, then

determines which mechanism will be most dominant and what the overall effect on dispersion performance will be.

THE EFFECT OF CARRIER SURFACE ROUGHNESS

The surface roughness of contacting particles determines their contact surface area and, with that, the interaction force between them. Given this basic fact it is not surprising that carrier surface roughness and its relation to dispersion performance has often been studied, or at least taken into account when studying the influence of other parameters (Fig. **2A**).

Different methods have been applied to measure carrier surface roughness. It can be quantitatively expressed as the ratio of specific surface area obtained by air permeametry or nitrogen adsorption to the calculated surface area of a volume equivalent sphere [19, 53, 55-58]. This ratio is sometimes referred to as the 'surface roughness index' (SRI). Alternatively, AFM has been used to determine the root mean square (R_{rms}) or average roughness (R_a) of a number of areas on different particles [59-70]. Other methods include laser profilometry [71] and image analysis [62, 72, 73]. Although these techniques enable a certain quantification of the carrier particle surface roughness, it is very difficult to distinguish between different types and scales of surface roughness. Furthermore, differences in fine particle content may strongly affect the results obtained.

The roughness of carrier surfaces is difficult to change independently from other carrier characteristics, which makes it difficult to determine its exact influence on dispersion performance. In many of the reviewed studies it is one of multiple characteristics that differ between carrier products of different grades or having undergone different treatment or production procedures. For example, it was found that recrystallised, freeze-dried or solvent treated mannitol improved the dispersion performance of salbutamol sulphate from FPFs of roughly 15% to 38-47% of the emitted dose [66, 69, 70, 74]. This was attributed to a smoother surface texture, as well as to a more elongated shape of the mannitol carrier particles. In contrast, the same group concluded that rougher surfaces are associated with better dispersion performance for lactose carrier particles of different grades or obtained by recrystallisation under different conditions [68, 73, 75, 76]. Besides carrier surface roughness, positive relationships between fines content and elongation ratio were also found for the lactose carriers. All studies from this group were performed with identical drugs, drug contents and blending and dispersion conditions. Although a certain influence of the carrier material on the effect carrier surface roughness in these studies cannot be excluded, other variables such as carrier shape (elongation ratio) and fines content may have been dominant too.

In several studies a solvent treatment procedure has been applied to smoothen carrier particles [53, 60, 70, 77, 78]. Young *et al.* managed to reduce the R_{rms} from 108.0 ± 36.8 to 26.5 ± 7.4 nm this way, but this resulted in only a negligible increase in the FPF from 13.46% to 14.16% of the emitted dose [60]. However, a slightly further reduction of R_{rms} to 12.2 ± 2.9 nm with the use of magnesium stearate resulted in an increase of the FPF to 58.4% of the emitted dose. Hence, the use of magnesium stearate, rather than a change in surface roughness, appeared to be the most dominant factor in this study, as was also noted previously by Zhou and Morton [7]. In addition, there might be a certain R_{rms} threshold above which a change in surface roughness is of lower relevance. An optimum surface treatment time of 10 minutes with an aqueous ethanol solution was found by Iida *et al*, which resulted in a decrease in R_a from 0.70 to 0.42 μm and an increase in the respirable fraction from 17.9% to 26.7% of the emitted dose [77]. A longer treatment time of 20 minutes did result in lower R_a of 0.37 μm, but also in a slight decrease of the respirable fraction to 24.5% of the emitted dose. In contrast, a reduction in dispersion performance with solvent treated lactose carrier particles was observed by Dickhoff *et al.*, but this was attributed predominantly to a reduction in fine lactose particle content [53].

The concurrent change in many other variables besides carrier surface roughness may have been less of a problem with a different approach introduced by Young *et al.* [65]. They produced 'composite' or granular carrier particles from spray dried primary particles with median sizes of 2, 6 or 10 μm. A trend of slightly increasing dispersion performance (FPFs ranging from 28% to only 31% of the emitted dose, significance not reported) with increasing R_{rms} (ranging from 0.32-0.50 μm) was observed, which the authors explained with a decrease in contact surface area and adhesion force between the drug and carrier particles. Interestingly, higher R_{rms} values were measured for the granular carriers composed of smaller primary particles. The small difference in FPF questions the relevance of surface roughness in the mentioned range. In the same study, a crystalline carrier with an R_{rms} of 0.09 μm resulted in an FPF of 21%. However, this carrier did not only differ from the granular carriers in surface roughness, but at least in shape too. Young *et al.* arguably affected the surface roughness mainly at a scale smaller than the drug particles, and their findings are, therefore, in line with the influence of carrier surface roughness on dispersion performance as proposed by Kawashima *et al.* [72]. They explained that this influence strongly depends on the scale of the surface roughness relative to the size of the drug particles. An increase in surface roughness from perfectly smooth to a certain nanoscale surface roughness would reduce the contact surface area between carrier and drug particles, which causes a lower adhesion force and improved dispersibility. A further increase in surface roughness to the microscale would result in a higher adhesion force due to the potential to form multiple contact points between the drug and carrier. A refinement of this hypothesis was proposed by Young *et al.*, who included the possibility of a distribution in surface roughness and the effects of surface roughness on physical mixture stability [64]. Given this premise, one would expect that a certain optimum in surface roughness exists in relation to dispersion performance. This is what Heng *et al.* concluded based on a comparison of similar sieve fractions from different lactose grades [59]. Unfortunately, the respirable fractions in this last study ranged from 10.25% to only 13.01%, and one may question the significance of the trend found.

Besides the effect on contact surface area between carrier and drug particles, other mechanisms have been proposed by which the roughness of carrier particles may affect mixture dispersion performance. It was found by Dickhoff *et al.* that granular carriers with increasing surface rugosity lead to higher drug detachment during dispersion than smoother crystalline carrier material [57]. They attributed this effect to a sheltering of the drug particles from press-on forces in the large carrier surface irregularities during mixing. In addition, they found an increase in the size of detached particles, which was indicative of drug agglomeration on the carrier surface during mixing. Because separation forces are generally higher for larger particles, this may have contributed to the observed effect on drug detachment. It was shown by the authors that these effects depend strongly on the drug content in the mixtures. Others have argued that a high degree of carrier surface roughness decreases the susceptibility of drug particles to particularly aerodynamic separation forces [17]. Although such mechanisms remain quite speculative, they do explain the interaction between carrier surface roughness and coarse carrier size, and its dependence on dispersion principle [21, 22], as discussed in the section on the effects of coarse excipient particles.

THE EFFECT OF DRUG CONTENT

The drug content in adhesive mixtures for inhalation is commonly between 0.1 and 4% by weight [42]. Although apparently narrow in absolute sense, this range of drug contents can correspond to carrier surface coverages varying from sub-monolayer to multilayer and to remarkable differences in dispersion performance. As for the other variables discussed up to this point the effects of

drug content on dispersion performance are not consistent and, therefore, not straightforward.

It was shown by Kulvanich and Stewart that increasing drug contents from 0.5 to 4% required a lower centrifugation speed to detach 50% of the total drug mass from glass carrier beads [34]. This was attributed mainly to the formation of agglomerates or multilayers by the drug component, which leads to higher centrifugal separation forces. Agglomerate formation was indeed observed by SEM in this study. Improved drug detachment with increasing drug content is in line with data presented by Zellnitz *et al.* [67]. They too used glass beads as carrier material and showed that higher FPFs were obtained as the carrier coverage increased from roughly 5 to 80%. The effect size depended on the type of treatment to which the surfaces of the glass beads were subjected, however. The highest fine particle fractions (up to 41.7% of the emitted dose) were obtained with mechanically treated glass beads, which exhibited a higher degree of 'nanoscale' surface roughness. In contrast to the findings of Kulvanich and Stewart and Zellnitz *et al.*, Young *et al.* found that dispersion performance (FPF) was largely unaffected by drug content for mixtures containing polystyrene beads with median sizes of 82 and 272 μm [29]. Only at the highest drug content tested (16.7% w/w, or 85% and 280% carrier coverage, respectively) the FPF was reduced from 20-23% to < 10% of the total dose. A polystyrene carrier with a median size of 582 μm did result in a trend of increasing FPF up to a drug content of 9.1% (i.e. a carrier:drug ratio of 10:1 or carrier coverage of roughly 300%), after which the FPF also declined. The authors explained the lowering of dispersion performance at the highest drug content with the formation of a segregated system, which supposedly contained poorly dispersible drug agglomerates. Unfortunately, the authors did not discuss the different trends observed for the different carrier sizes.

Inconsistent findings regarding the effects of drug content on dispersion performance have also been obtained for carriers with less uniformly smooth surfaces, such as lactose. Steckel and Müller determined the dispersion performances of formulations containing 1%, 5% or 9% of budesonide [79]. A general trend of decreasing FPF with increasing drug content was observed, with the absolute difference being maximally 21.9%. This trend was most pronounced going from 1% to 5% of drug. The underlying mechanisms were not investigated or discussed. In another study Steckel *et al.* obtained consistently higher fractions < 5 μm for formulations containing 2.8% instead of 0.25% of salbutamol sulphate [80]. This trend was observed for different lactose carrier grades and for two different inhalers (the Aerolizer and Easyhaler). It was speculated by the authors that this was due to the saturation of active sites, as discussed in the section on fine excipient particles. Further evidence for the saturation of active sites on lactose carrier surfaces with increasing drug content was provided by Young *et al.* [81]. They showed that, up to a threshold of 0.27%, an increase in drug content resulted in a lower FPF as the fine particle dose remained constant. A further increase in drug content beyond this threshold resulted in a trend of increasing FPF. The authors attributed this to the preferential occupation of active sites by the drug particles. At the threshold drug content, the maximum binding capacity of active sites would be reached and any additional drug particles would bind to sites of lower activity and, therefore, be more easily dispersed. The agglomeration of drug particles with increasing drug content beyond the threshold value was considered as a potential cause for improved dispersion by the authors. However, the authors stated that no evidence to support this mechanism was found with SEM imaging, and that such a mechanism would be unlikely considering the balance of adhesive and cohesive forces for a lactose-salbutamol system. In a follow-up study, it was shown that a smoothing of the lactose carrier particles resulted in a lowering of the drug content threshold beyond which the FPF increased from 0.27% to 0.13% [82]. This was considered a result of the reduction of the binding capacity of active sites. Based on drug detachment experiments, de Boer *et al.* also concluded that active sites are likely saturated with an increase in drug content [83]. They found that the residual carrier surface payload after dispersion at high flow rates reached a plateau with increasing drug content. However, this plateau, which was considered indicative of the saturation of active sites, was achieved at much higher drug contents of 3 to 4% than the threshold values determined by Young *et al.* and Sabawi *et al.* Such a difference may partly be caused by batch differences between the lactose carrier material used, and by differences in the mixing and dispersion conditions in the studies. Albeit speculative, the saturation of active sites does provide a logical explanation for a difference in effect at different drug content ranges. In a study by Le *et al.*, different effects of drug content were also observed between formoterol in the content range of 0.09 to 0.17% and fluticasone in the range of 2 to 5% [84]. However, now a trend of decreasing FPF was obtained for fluticasone over the higher drug content range, whereas the FPF of formoterol increased over the mentioned lower content range. The authors attributed the decrease in FPF of fluticasone to the formation of agglomerates, which would be difficult to disperse. No further evidence to support this hypothesis was provided by the authors.

Another level of complexity regarding the effects of drug content is introduced by regarding its influence on the susceptibility of drug particles to frictional and compressive forces during the mixing process. It was suggested by several authors that, as the drug content increases, drug particles fill up carrier surface irregularities and may become more in reach of the mixing forces [24, 25, 33, 57]. This could affect the agglomeration behaviour of the drug, its compression onto and its redistribution over the carrier surface. Note that such a mechanism is not likely to play a role with perfectly smooth, spherical carrier particles discussed earlier in this section. Much of the evidence in support of these mechanisms is empirical and stems from experiments in which drug detachment from the carrier surface during dispersion was studied. Differences in the mode [25] and rate [33] of drug particle detachment depending on drug content, as well as interactions with variables such as carrier surface roughness, mixing time and inhalation flow rate [24, 42, 57] can all be well explained with a combination of the different mechanisms mentioned throughout this section. Grasmeijer *et al.* suggested that, because the different mechanisms in play can result in different effects following a change in drug content, the overall effect of a change in drug content on dispersion performance is determined by the balance of these mechanisms [42]. It was furthermore suggested that this balance can be shifted by a different choice for one of the interacting variables, even for dispersion variables that do not alter the mixture properties (such as the inhalation flow rate [85]). Although the results of dispersion experiments as well as interactions with other variables could be well explained this way, the exact relevance or contribution of the different mechanisms in play could not be established using SEM or laser diffraction techniques [42].

A certain similarity exists between the mechanisms by which fine excipient particles and drug content exert their effect on dispersion performance. This similarity is expressed in the 'total fines concept' introduced by Thalberg *et al.*, who showed that the dispersion behaviour of formulations with different fine excipient particle and drug contents could be well modelled by considering their total fine (drug and excipient) particle content and the cohesive energy of the fine particles [86]. Grasmeijer *et al.* later confirmed that a strong similarity exists between the effects of fine excipient and drug particles, but that this is strongly dependent on their similarity in size distribution [40]. These findings indicate that, notwithstanding all the inconsistencies throughout the literature, common grounds can be found between the effects of different variables.

THE EFFECT OF CARRIER, DRUG AND FINE EXCIPIENT MATERIAL

The majority of studies on adhesive mixtures for inhalation have been performed with the carrier and drug materials that are most common in marketed formulations: lactose and salbutamol sulphate or budesonide (Figs. **3A**,**B**). However, particle properties and interaction energies between the constituents of adhesive mixtures may be material dependent to a great extent. This could affect the processes that occur during mixing, the strength of co- and adhesive interactions and, ultimately, mixture dispersion performance. One of the challenges associated with the testing of different carrier, drug or fine excipient materials is yet again that interactions and a number of linked parameters can affect the results obtained. The particle size distribution (including the fine particle content), particle shape distribution, particle surface roughness and hygroscopicity are just a few examples of the factors that may contribute to differences in dispersion performance between different materials. Needless to say this will greatly complicate the drawing of unequivocal conclusions.

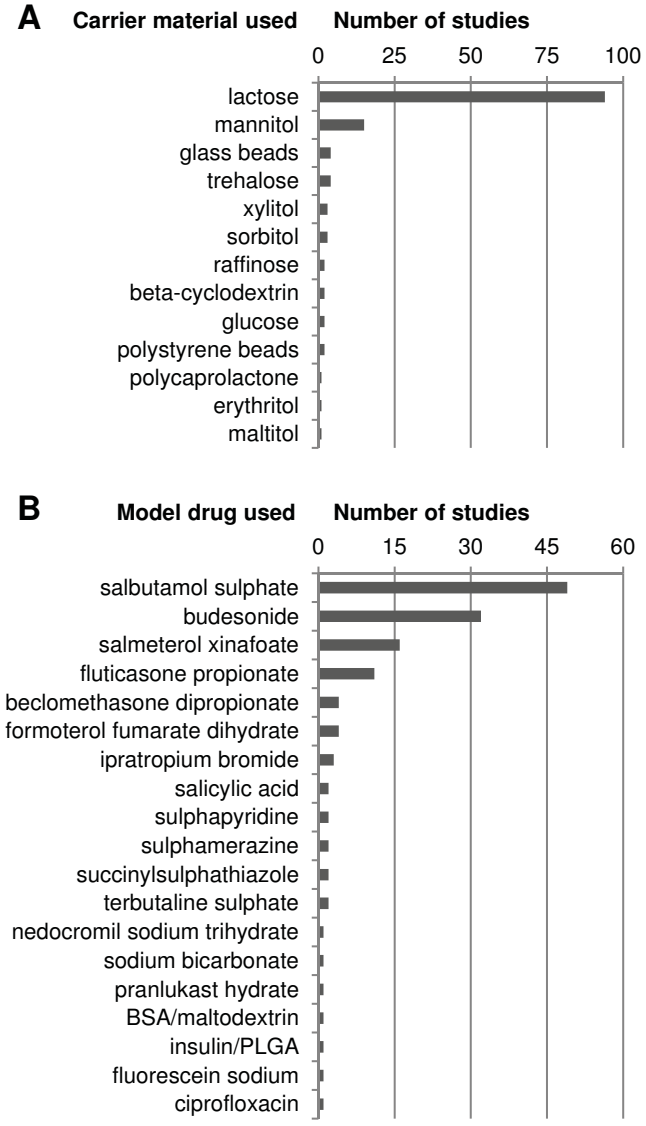

Fig. (3). Frequency of use of different carrier materials (A) and model drugs (B) throughout the literature. References included in the characteristics: [5, 8-29, 31-35, 38-42, 44-49, 51-53, 55-84, 86-89, 91-95, 97-99, 102, 104, 109-133].

The dispersion performances of binary and ternary mixtures containing lactose, mannitol or sorbitol excipient materials was tested by Tee *et al.* [87]. Differences in dispersion performance between binary mixtures containing these sugars as the carrier material were minor, with FPFs ranging between 6.4% and 9% of the recovered dose. Furthermore, these authors found that the type of sugar did not play an important role in determining the effect of added fine excipient particles. In contrast, major differences in dispersion performance between different sugar carrier materials were observed by Steckel *et al.* [88]. They used different grades of mannitol, glucose, sorbitol, maltitol and xylitol and obtained FPFs of salbutamol sulphate roughly between 2% and 50% of the total dose. The best dispersion performance was obtained with mannitol, but the variability in dispersion performance between different grades of the same sugar was of the same order of magnitude as that between the different sugars. It was concluded by the authors that especially the more hygroscopic sugar alcohols sorbitol, xylitol and maltitol resulted in a poor dispersion performance. A similar conclusion was also drawn by Adi *et al.*, who found a trend of decreasing dispersion performance with increasing water content between lactose, glucose, mannitol and sorbitol [89]. The highest FPFs of salmeterol xinafoate were obtained with glucose and mannitol as the carrier material (still only 12% and 10% of the recovered dose, respectively) by these authors. Unfortunately, the authors did not provide details about the water content determination, so it is unclear whether differences in water of crystallisation between the carrier materials have been taken into account. Nevertheless, the relationship between moisture content and dispersion performance may be an indication that differences in dispersion behaviour between carrier materials may to a large extent result from differences in capillary interactions or electrostatic behaviour. In contrast to Tee *et al*, Adi *et al.* did obtain remarkable differences in the magnitude of effect between the different sugars when used as fine, tertiary component.

One of the factors that is influenced by the types of constituent materials in adhesive mixtures and that has received a fair amount of attention in the literature is the ratio of cohesive to adhesive interaction forces. The so-called cohesion-adhesion balance (CAB), which can be obtained by AFM [90], is a measure of the relative adhesive or cohesive tendency of a certain drug-excipient combination. A CAB value < 1 indicates that a drug is less cohesive to itself than adhesive to the carrier material, whereas a CAB value > 1 indicates that a drug is more cohesive than adhesive. It was suggested that predominantly cohesive drugs would be more prone to form agglomerates or resist deagglomeration during mixing, resulting in more inhomogeneous mixtures that are also sensitive to segregation [91]. Although the CAB value in principle is not a measure of the absolute magnitude of cohesive or adhesive interaction forces within the mixture, exceptionally low or high values could be an indication of strong adhesive or cohesive interactions, respectively. Large differences in the dispersion performances of adhesive mixtures with β cyclodextrin, lactose, raffinose, trehalose or xylitol as the carrier material were obtained by Hooton *et al.*, with salbutamol sulphate FPFs ranging from 31.4% to 0.8% for the order in which the sugars are mentioned [92]. They found a trend of increasing dispersion performance with increasing CAB values from 0.3 to 1.6. Evidence for a difference in the structure of the blends was limited to SEM images and content uniformity data, which indicated that lower CAB values resulted in a better distribution of the drug over the carrier surface and more homogeneous mixtures. The authors acknowledged that factors such as particle morphology, surface roughness and fine particle content may have affected the relationship between CAB and dispersion performance for different carrier materials. This is likely why a similar relationship was not found by Jones *et al.* when categorising the CAB-dispersion performance data of 16 different sugar-drug combinations (four different sugars and drugs) by the type of drug [93]. Only when these data were categorised by carrier material, so as to eliminate differ-

ences in carrier morphology, roughness and particle size distribution, a trend was obtained in which a slightly cohesive CAB (roughly between 1 and 1.2) resulted in the highest fine particle dose. The authors explained this finding by stating that slightly cohesive CAB values might be indicative of relatively weak drug-carrier adhesion interactions and the formation of more easily detachable drug agglomerates that are not too strong to be dispersed into primary particles. Unfortunately, this plausible explanation was not further corroborated by the authors with studies on formulation structure. A possible difference in moisture content between the carrier materials was not regarded in this study. A great difference in the agglomeration behaviour during mixing between fluticasone propionate and salmeterol xinafoate was demonstrated by Grasmeijer *et al.*, which they could explain with CAB values previously presented in the literature for these drugs [31]. The authors did not measure CAB values of their own batches of starting material, however, even though it is known that these values can be strongly batch dependent. Nevertheless, the above findings are an indication that the balance in strength of cohesive and adhesive interactions may under certain conditions play an important role in adhesive mixtures for inhalation. As already briefly discussed in the section on the effects of fine excipient particles, the CAB of drug-fine excipient combinations was also found to play a role in mixture dispersion performance, with more adhesive combinations (lower CAB values) being more favourable [47].

It is not only the type of drug or sugar that may affect mixture dispersion performance, but also their different crystal habits or (pseudo-) polymorphs. For example, Traini *et al.* prepared mixtures with different forms (α-, β-, anhydrous and monohydrate) of lactose and obtained FPFs ranging from 5.5% to 19.8% of the total dose [94]. On a side note, a strong inverse linear relationship (R^2 = 0.977) between FPF and total surface energy of the carrier material, as determined by inverse gas chromatography (IGC), was found in this study, whereas differences in fine particle content between the carrier materials did not show the expected relationship to FPF. Further examples include a study by Hooton *et al.*, who obtained different CAB values depending on the crystal face of budesonide used for interaction experiments by AFM [95]. Rehman *et al.* applied different conditions for the super critical fluid crystallisation of terbutaline sulphate, which resulted in FPFs ranging from 11.4% to 38.6% of the total dose [96]. The authors unexpectedly measured a lower surface energy for a semi-crystalline form of the drug than for a fully crystalline form, which also resulted in the best dispersion performance. Kubavat *et al.* showed that different crystallisation conditions for budesonide and fluticasone propionate resulted in different Young's moduli of the starting materials, a different milling behaviour and slightly different CAB values after milling [97, 98]. The differences in dispersion behaviour were only minor, however, with FPFs of the emitted dose ranging from 7.2% to 9.7% and 8.3% to 10.5% for binary mixtures containing the different budesonide or fluticasone batches, respectively. A similar CAB, mechanical behaviour and dispersion performance were obtained for the anhydrous and monohydrate form of ipratropium bromide [99]. Despite the small differences in dispersion behaviour found in the latter studies, it may not be excluded that the mechanical properties of the drug play a role in mixture dispersion performance. They will determine its response to the mechanical stresses applied during mixing, which can lead to significant plastic deformation of the constituent particles [31]. Lam and Newton furthermore found that an increase in geometric median adhesion force with applied compression force for pharmaceutical powders on a surface of stainless steel was most pronounced for materials with a lower yield stress [100]. For the same reason it may not be unreasonable to think that especially softer drug materials, perhaps even relative to the hardness of the carrier material, could be more predominantly cohesive and, therefore, prone to agglomeration.

DISCUSSION

So, given the preceding, can we conclude that adhesive mixtures for inhalation are not fundamentally understood? Most certainly adhesive mixtures for inhalation are very complex formulations. This review supports previous statements that interactions between formulation and dispersion variables play an important role in determining the dispersion performance of adhesive mixtures [2, 4, 5]. In fact, (multi-order) interactions between variables of the formulation and dispersion process are omnipresent, with many apparently inconsistent findings as a result. It is, therefore, not difficult to lose track of the common grounds between observations and to simply conclude that we do not fundamentally understand adhesive mixtures for inhalation. On the other hand, the realisation that interactions between formulation and dispersion variables are omnipresent is an important step towards such a fundamental understanding. In addition, for many of the observed effects and interactions rational explanations have been given. These explanations more often than not remain very speculative, however, and the challenge therefore lies in proving their truth.

A consequence of the interactions between formulation and dispersion variables is that not one variable is dominant over others in determining dispersion performance under all conditions. In other words, the main variables affecting dispersion cannot be identified, because many of the variables relevant to dispersion performance may be dominant for certain formulation and dispersion conditions applied, and become subordinate when these conditions are changed. Therefore, the remainder of this discussion will focus on understanding the interplay between variables relevant to dispersion performance, rather than trying to identify those variables that are most important.

A Proposed Theoretical Framework of the Interplay Between Variables

Principal Factors and Effects

One of the common grounds between all studies reviewed is that effects on dispersion performance of formulation variables can often be mechanistically explained with changes in only a few different mixture properties, which we propose to be the following:

1. the size distribution of the drug particles (including drug/drug and drug/fine excipient agglomerates) as they are detached from the carrier surface during dispersion;
2. the degree of compression of the drug particles onto the carrier surface and each other during mixing,
3. the distribution in 'activity' of carrier sites that are occupied by drug particles; and
4. the tensile strength or fluidisation behaviour of the mixture.

We shall refer to these mixture properties as the 'principal factors' of the mixture [101]. They have the potential to affect the adhesion and separation energy distributions of the drug throughout the mixture during dispersion, and, with that, mixture dispersion performance [36, 50, 51, 85, 100, 102]. Especially the first three factors will depend strongly on the inertial and frictional forces that are exerted on the powder particles during the blending process. Effects on dispersion performance through a change in the principal factors listed will be referred to as the principal effects, being particle size, press-on, activity and fluidisation effects, respectively. They are explained in more detail in the following sections.

Particle Size Effects

The relationships between drug particle size and the magnitude of adhesion and different types of separation forces are well established [36, 103]. The adhesion force is generally proportional to the drug particle diameter ($F_{ad} \propto d_{drug}$), whereas the separation force may be proportional to a higher power of $d_{drug,}$ depending on the predominant type of separation force generated during inhalation.

As a result, a positive correlation between drug particle size and drug detachment from carrier particles can be expected, and such expectations have been experimentally confirmed in several studies [34, 35, 104]. Because of these considerations it is not surprising that a change in the particle size distribution of the drug, either by its (de-) agglomeration during mixing or its co-agglomeration with a ternary component (fines), is part of hypotheses that explain the effects on dispersion performance of many of the variables reviewed. Because not all types of separation forces are proportional to the same power of d_{drug}, the dispersion principle may determine the relevance to dispersion performance (the principal or particle size effect) of a certain change in the particle size distribution of the drug as it is detached from the carrier (the principal factor), For example, theoretically one may expect that the co-agglomeration of a drug with added fine lactose particles will be more relevant to drug detachment for inhalers relying on inertial separation forces ($\propto d_{drug}^3$) than for those relying on aerodynamic drag forces ($\propto d_{drug}$ or d_{drug}^2).

The particle size distribution of the drug particles as they are detached from the carrier surface is a complex powder characteristic that depends on many variables, such as the primary particle size distribution of the drug and its degree of agglomeration with other drug particles or a ternary component. It may not even be similar to the drug particle size distribution as it is present on the carrier surface, depending perhaps also on the magnitude and type of dispersion forces applied. Characterising this property for that reason alone will be very challenging, but considering its theoretical and experimentally confirmed relevance, it may well be worth pursuing.

Press-on Effects

The strength of adhesive or cohesive bonds may be affected by a compression force applied onto the contacting materials during or after bond formation. This holds true for pharmaceutical powders, as was shown by Lam and Newton [100]. They found a linear increase in geometric median adhesion force with applied compression force for polyethylene glycol, lactose, starch and calcium carbonate on a surface of stainless steel. Others have reported a similar relationship between compressive force and adhesion force for micronised powders of lactose, salmeterol xinafoate and budesonide [102, 105, 106]. During mixing, drug particles may be compressed onto the lactose carrier surface by a vector component of the mixing forces that is directed towards the carrier surface. The mixing forces are then mostly referred to as 'press-on forces'. These press-on forces likely increase the average drug-carrier adhesion force, which lowers the chance of drug particle detachment from the carrier surface during inhalation. As discussed in this review, press-on forces are thought to play an important role in the effects of numerous formulation variables, such as drug content, mixing time, carrier size distribution and the size distribution and content of added fine lactose particles. Basically, these variables are suggested to (partly) affect dispersion performance through an influence on the susceptibility of drug particles to press-on forces, the magnitude of these forces or the number of 'compression events' during the mixing process.

Activity Effects

As already briefly mentioned in this review, two distinctly different definitions for the 'activity' of carrier surface sites currently exist. They differ mainly in whether or not they regard an influence of the carrier surface on the magnitude and efficiency of the forces separating the drug particles from the carrier during dispersion [1, 50, 81].

Regardless of the definition applied, carrier surface site activity is a very complex parameter that includes factors such as surface roughness, surface chemistry (including contaminations) and surface free energy. Due to the inhomogeneous nature of carrier surfaces with regard to such aspects it is generally accepted that a distribution exists in the activity of surface sites on carrier particles [50, 81]. Therefore, the spatial distribution of the drug particles over carrier surfaces too determines the activity distribution of carrier surface sites occupied by drug particles.

Not surprisingly, changes in the activity distribution of occupied carrier surface sites play an important role in the 'active sites hypothesis'. As discussed, this hypothesis is often used to explain the effects on dispersion performance of changes in drug and, particularly, fine excipient content [37, 44, 81, 83]. However, not only effects on dispersion performance through the saturation of active sites by drug or fine excipient particles can be considered activity effects. They may also include, for instance, changes in dispersion performance due to changes in the spatial distribution of the drug over the carrier particles; changes in the surface roughness (distribution) of the carrier particles; or the coating of the carrier particles with excipients such as magnesium stearate, as explained in more detail elsewhere [50].

It was suggested previously that the type of dispersion principle used may strongly affect carrier surface site activity or its relationship to dispersion performance [50]. For example, in contrast to inertial separation forces, the susceptibility of drug particles to aerodynamic separation forces may be strongly reduced by a higher degree of macro scale roughness of the carrier surface [17]. Therefore, interactions between the dispersion principle and variables that affect dispersion performance predominantly by activity effects can be expected.

Fluidisation Effects

As discussed, the fluidisation behaviour of adhesive mixtures may affect dispersion performance by an influence on the energy available for dispersion and the number of particle-particle collisions [51]. Studies on the relevance of this mixture property to dispersion performance and its underlying mechanisms are scarce, but an influence of the design of the dosing and dispersion principle of the inhaler on the relevance of the mentioned effects may be expected. For example, Sims *et al.* have shown that powder entrainment from a Rotahaler not only depends on the lactose grade used, but also on the presence of a split capsule [107].

Please note that the list of principal factors may not be complete and the distinction between several of these factors may be arbitrary. For example, in relation to factor 1, also the strength of drug/drug or drug/fine excipient agglomerates will be important to dispersion performance. For the purpose of obtaining a general idea of how variables of the formulation and dispersion process and mixture dispersion performance relate to each other the given examples will do, however.

A formulation variable may affect only one principal factor, or, more likely considering the reviewed literature, multiple factors at once. In case of the latter, the effect on dispersion performance will be determined by the overall balance or sum of the principal effects mentioned. In addition, interactions between variables can be considered a change in the sum of the principal effects.

Types of Interactions

To aid in the understanding and identification of interactions we propose to differentiate between two distinct types, both of which have been encountered in the reviewed literature:

1. interactions in which the relevance to dispersion performance of certain effects of a variable on the principal factors of the mixture is affected by another variable, and
2. interactions in which variables affect each other in how they alter the principal factors of the mixture.

These descriptions may appear very cryptic at first, but they can be more easily understood from the following examples.

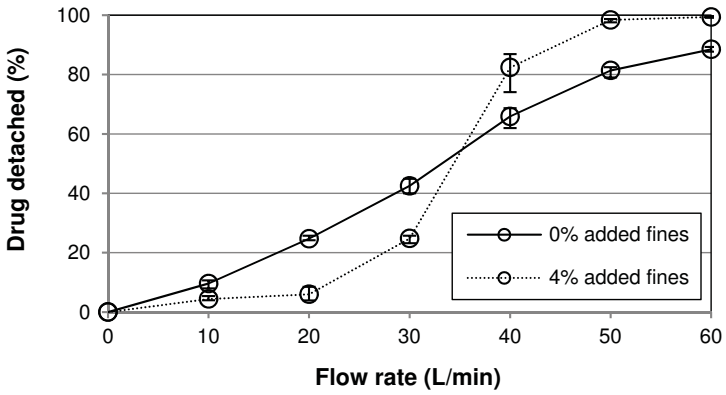

Fig. (4). Budesonide detachment from the lactose carrier during dispersion at different flow rates for mixtures with and without added lactose fines. Data adopted from Grasmeijer *et al.* [40].

Fig. **4** shows the relative amount of drug that detaches from the lactose carrier during dispersion at different inhalation flow rates for two formulations. The formulations only differ in their added lactose fines content and the effect of that on dispersion performance is dramatically different between flow rates of 20 and 50 L/min. Hence, the relevance of the difference in the mixture properties (principal factors) to dispersion performance is affected by the inhalation flow rate. This is an example of a type 1 interaction. These interactions can not be identified based on differences in physical powder properties. Interactions with inhalation flow rate have been reported for other formulation variables as well, such as the mixing time and drug content [31, 42], and it was previously argued that they should be expected for any variable that changes the powder properties [85]. Besides inhalation flow rate, also the dispersion principle can cause a type 1 interaction. This was demonstrated by Donovan and Smyth and Hagedoorn *et al.* for the effect of coarse carrier size [22, 30], and we have explained this for the relevance of particle size and activity effects in general in this discussion.

It can also be that a similar change in one formulation variable causes a different change in the powder properties (principal factors) depending on another variable, and as a result affects dispersion performance in a different way. A clear example can be found in a study by Grasmeijer *et al.* who found a notable degree of agglomeration of salmeterol xinafoate on the surface of coarse carrier particles with prolonged mixing, but not so much when a finer carrier fraction or fluticasone propionate were used instead (see Fig. **5**) [31]. It was suggested that primarily these differences in the particle size distribution of the drug on the carrier surface were responsible for a different effect of mixing time on dispersion performance at a low inhalation flow rate of 20 L/min. This is an example of a type 2 interaction. In contrast to type 1 interactions, type 2 interactions are reflected in the mixture properties and can, therefore, be identified by studying the powder structure with the appropriate techniques. In our example, the finer carrier is thought to prevent the notorious agglomeration of salmeterol during mixing due to its smaller carrier surface irregularities in which the agglomerates can be formed. Fluticasone on the other hand, is a less cohesive drug than salmeterol, which supposedly reduces its tendency to agglomerate during mixing. Because differences in formulation variables represent the majority of methodological differences between the formulation studies reviewed, most of the interactions encountered are likely of the second type.

The interplay between variables as proposed throughout this section is summarised schematically in Fig. **6**.

Major Challenges and Future Research Directions

From the proposed interplay between variables presented in Fig. **6** it follows that the mixture properties (principal factors) are intermediary between the properties of the starting materials and the mixing process on the one hand, and the dispersion behaviour of adhesive mixtures on the other. The ability to accurately measure the principal factors of adhesive mixtures will, therefore, be a prerequisite to the unravelling of the relationships between these types of formulation variables and mixture dispersion performance. This requires a thorough understanding and definition of the principal factors (especially carrier surface site activity), and the development of new or improved characterisation techniques for them. Promising in this regard are, for example, chemical-selective imaging techniques, such as those based on Raman imaging. They may enable the accurate determination of the distribution and agglomeration behaviour of the drug component throughout adhesive mixtures [48, 108]. The spatial distribution of drug particles on carrier surfaces after the dispersion process may lead to a better insight in what constitutes active sites [50]. It was furthermore suggested that the degree of compression of drug particles during mixing may be indirectly measured based on changes in the drug's apparent solubility [31, 54]. Also the consolidation and compaction behaviour of the fines components (drug and fine excipient particles) could be a relevant aspect to consider, as it was hypothesised that the formation of coherent fine particle networks is an important factor in determining mixture dispersion performance under certain conditions. This may be assessed, for example, by the use of very small ring shear testers.

In relating properties of the starting materials to the mixture properties and ultimately dispersion performance, it is very important to realise that these properties may be subject to change during the mixing process. For example, it was shown that mixing can lead to the plastic deformation of drug particles or the formation of fine excipient particles due to attrition of the carrier material [31, 51]. This may diminish the relevance of initial characteristics of the starting materials, such as their size and shape distribution, surface free energy distribution, CAB or surface roughness. Other properties that determine the response to the mechanical stresses during mixing, such as hardness or yield strength, may be more relevant in these situations.

The reviewed literature has shown that, besides interactions, linkage between variables is a major complicating factor in obtaining a fundamental understanding of adhesive mixtures. More often than not, variables simply cannot be changed individually, not even in idealised situations such as with the use of perfectly smooth carrier particles. A high sense of awareness of this fact by researchers is required in order to prevent the drawing of incorrect conclusions or the focussing on aspects of secondary importance.

Finally, it is unlikely that the engineering of adhesive mixtures for inhalation alone will lead us to efficient low dose dry powder inhalation systems. In all the reviewed literature, reported FPFs did not exceed 58% of the emitted dose or 49% of the nominal dose

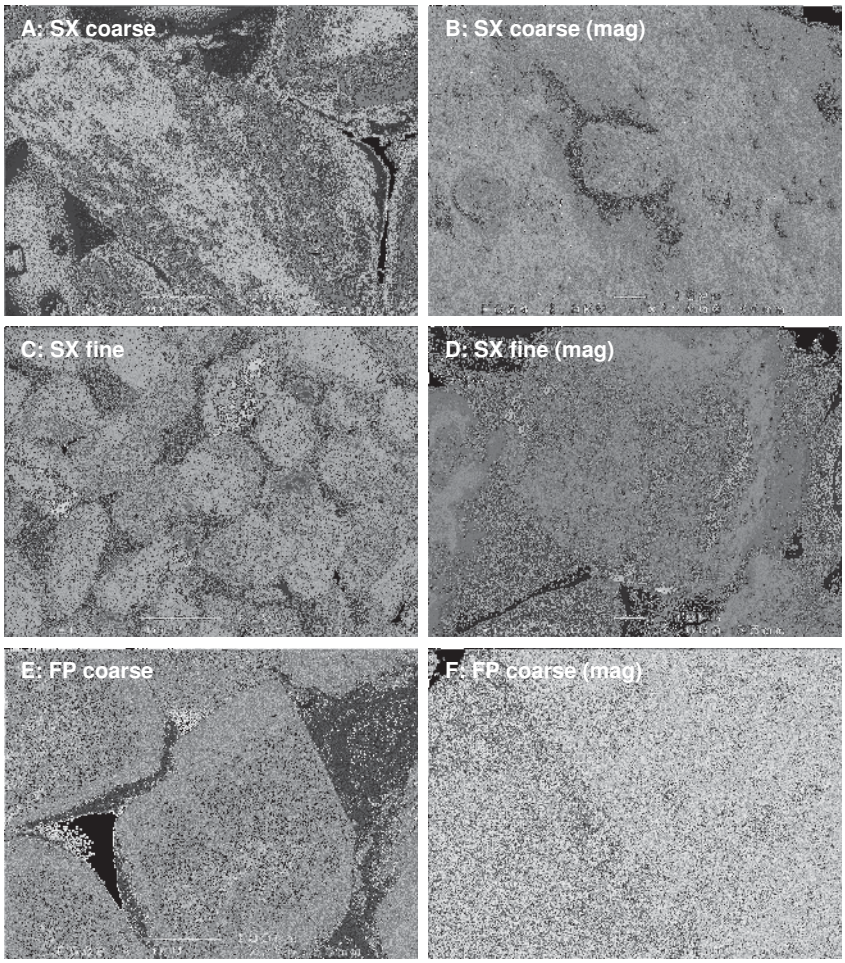

Fig. (5). Differences in drug agglomeration behaviour under different formulation conditions. A+B: images showing large salmeterol xinafoate (SX) agglomerates on the surface of a coarse lactose carrier (250-315 μm) particle. **C+D:** images showing relatively small SX agglomerates on a fine lactose carrier (63-90 μm). **E+F:** images showing relatively small fluticasone propionate (FP) agglomerates on a coarse lactose carrier (250-315 μm) particle. All mixtures were prepared using the same mixing conditions (i.e. 90 rpm for 420 minutes in a Turbula blender). Images A,B, D, E and F are obtained from Grasmeijer *et al.* [31].

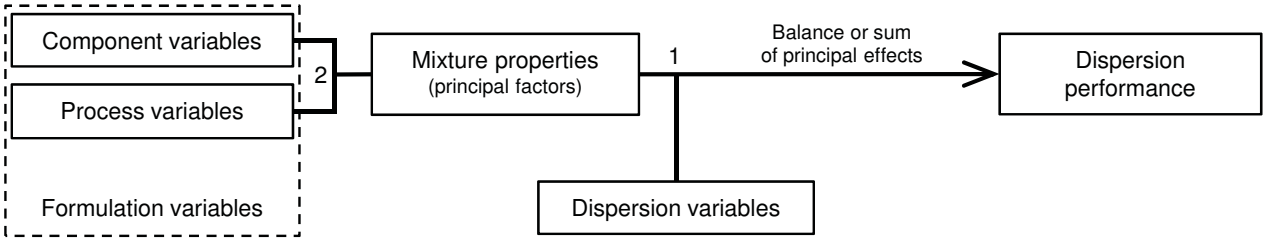

Fig. (6). Schematic presentation of the interplay between variables in the formulation and dispersion of adhesive mixtures for inhalation. Component variable: any variable related to the physicochemical properties and relative amounts of mixture components (e.g. carrier surface roughness, carrier PSD, type of drug, drug content). **Process variable:** any variable related to the mixing and mixture handling processes (e.g. mixing time, mixing intensity, mixing principle, batch size, powder filling or dosing principle). **Dispersion variable:** any variable related to the dispersion process (e.g. type of dispersion principle, inhalation flow rate, loading of the dispersion principle or dose weight). The principal factors and effects are listed in the text. The numbers 1 and 2 refer to the different types of interactions, as explained in the text.

(Table **1**). The development of more effectively dispersing inhalers will, therefore, likely be an important aspect in this regard as well.

CONCLUSION

Many inconsistent findings between studies on adhesive mixtures have led to the perception that this type of formulation is not fundamentally understood. In recent years it has become clear that these inconsistent findings are mostly the result of interactions between the variables that are relevant to formulation dispersion performance. As a result, not one aspect of the starting materials will be dominant over others in determining mixture dispersion performance under all conditions. Engineering adhesive mixtures for inhalation will, therefore, mostly be a matter of understanding and controlling these interactions. Based on the reviewed literature, we here propose a theoretical framework in which two distinct types of interactions between formulation and dispersion variables are iden-

Table 1. Minimum and maximum fine particle fractions of adhesive mixtures reported in the reviewed literature. FPF_{ed} = fine particle fraction of the emitted dose; FPF_{nom} = fine particle fraction of the nominal or recovered dose; n = number of studies included in the statistic. Individual studies are included in only one of both categories, depending on the type of FPF reported. Studies for which it is not clear based on what part of the dose the FPF was calculated are not included.

	min (%)	$min_{average}$ (%)	max (%)	$max_{average}$ (%)	n
FPF_{ed}	1.0	13.2	58.0	37.4	39
FPF_{nom}	0.3	8.5	49.0	23.5	44

tified. According to this framework, the mixture properties, rather than the properties of the starting materials, are key to obtaining a further understanding of these interactions and of adhesive mixtures for inhalation in general. We therefore suggest that a sharper focus on the identification, definition and analysis of these properties in the years to follow may be desirable. In addition, it is unlikely that efficient low dose dry powder inhalation systems based on adhesive mixtures will ever be developed without a concurrent effort to improve the efficacy of dry powder inhalation devices.

CONFLICT OF INTEREST

The employer of PH, HWF and AHdB receives royalty income over the sales of Novolizer®, Genuair® and Pressair® inhalers.

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