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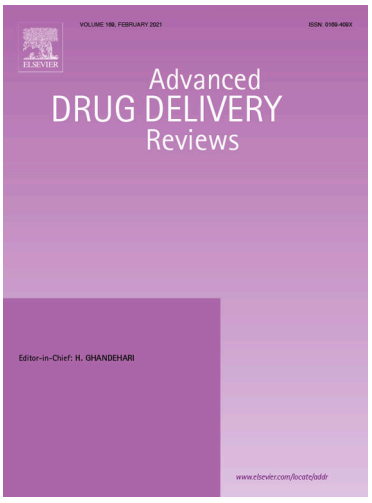

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Recent developments in lactose blend formulations for carrier-based dry powder inhalation

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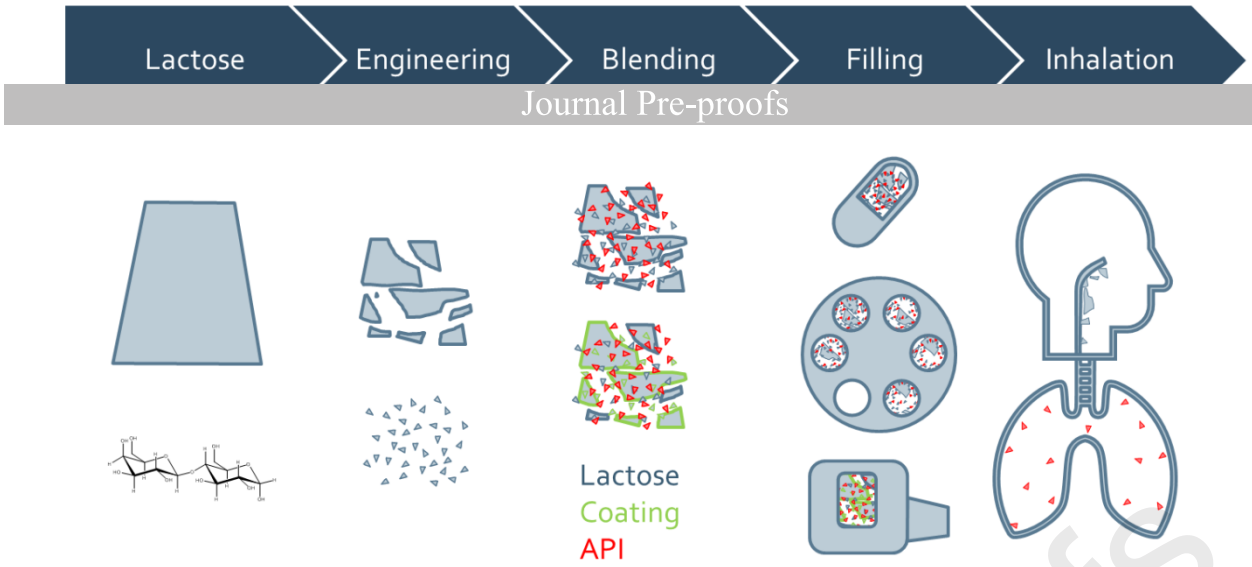
Abstract

Lactose is the most commonly used excipient in carrier-based dry powder inhalation (DPI) formulations. Numerous inhalation therapies have been developed using lactose as a carrier material. Several theories have described the role of carriers in DPI formulations. Although these theories are valuable, each DPI formulation is unique and are not described by any single theory. For each new formulation, a specific development trajectory is required, and the versatility of lactose can be exploited to optimize each formulation. In this review, recent developments in lactose-based DPI formulations are discussed. The effects of varying the material properties of lactose carrier particles, such as particle size, shape, and morphology are reviewed. Owing to the complex interactions between the particles in a formulation, processing adhesive mixtures of lactose with the active ingredient is crucial. Therefore, blending and filling processes for DPI formulations are also reviewed. While the role of ternary agents, such as magnesium stearate, has increased, lactose remains the excipient of choice in carrier-based DPI formulations. Therefore, new developments in lactose-based DPI formulations are crucial in the optimization of inhalable medicine performance.

Keywords

Lactose, DPI, carrier, blending, powders

Graphical abstract



1. Introduction

Lactose monohydrate has a long and proven history in the formulation of carrier-based dry powder inhalers. It is by far the largest, if not the only, commercially utilized and safe excipient in this field.

formulations are made, from design of the carrier, blending with active ingredients, to filling of devices, in the effort to achieve a functional dry powder inhalation (DPI) formulation. In Section 2, the functionality and engineering of lactose grades in DPI formulations are discussed, demonstrating the role of carriers in the process. In Section 3, the blending process of lactose carriers with active pharmaceutical ingredients (APIs) to achieve functional blends is demonstrated. Section 4 focuses on the filling of DPI devices with blends of lactose and API.

1.1. Historical perspective of carrier-based DPI

The inhalation of medications to the lungs has a long history and can be achieved in various ways [1,2]. Exploiting the pathway via the lungs has several advantages, such as bypassing the first-path metabolic pathway and, in cases of lung diseases such as asthma or COPD, directly targeting the therapeutic area [3]. The disadvantage of inhalation is that the respiratory system is designed to prevent powder and particles from reaching deeper into the lungs. To reach the alveolar region in the lungs, particles need to have an aerodynamic diameter on the order of 1–5 µm. Smaller particles have a high probability of being exhaled, and larger particles would be impacted in the mouth or on the walls of the higher airways [4]. This implies that formulations for drug delivery to the lungs require medication with a very small particle size distribution (PSD). The cohesive nature of drug particles results in the formation of larger agglomerates that are not within the desired size range. Furthermore, the flowability of such cohesive powders is generally very poor, leading to issues in handling. These issues can be solved in various ways, such as through nebulization of a liquid suspension or solution, dispersion or solution in a propellant in a pressurized metered dose inhaler (pMDI), or by use of a carrier material in dry powder inhalers. For dry powder inhalers, the carrier material is generally lactose [5], which is the focus of this review. Each technology has its advantages and disadvantages. Nebulization of drugs requires prolonged inhalation. However, pMDIs and DPIs lack this disadvantage, and a single inhalation event is generally sufficient to deliver a complete dose to the lungs. Historically, pMDIs have included propellants such as chlorofluorocarbons (CFCs), which were banned by the Montreal protocol in 1989 because of their ozone-depleting effect. This has led to the development of alternative, less harmful propellants, such as hydrofluorocarbons (HFAs) and to the accelerated development of carrier-based dry powder inhalers [1,6–8] in the 1990s. Recent developments indicate that even low-burden HFAs

are now on the horizon for replacement [9,10], which will result in another boost to the evolution of DPI.

Dry powder inhalers have existed for many years and have included the use of carriers to facilitate aerosolization [1]. In 1971, Bell et al. [11] mentioned lactose as a carrier, using a coarse grade to facilitate the poor flow of fine powders. From that date until 2022, over 650 papers were published with the terms “dry powder inhaler” and “lactose” in the title or abstract, according to a search in Scopus®. There has been a steep increase in DPI-related papers since the early 1990s, that is, after the Montreal protocol. In the early 2000s, GSK launched the commercially most successful carrier-based DPI device, Advair/Seretide Diskus®, with lactose monohydrate as the carrier ingredient.

Dry powder inhalers are medical devices that contain dosage in dry powder form. For administration, the appropriate amount of powder needs to be metered, followed by dispersion of the dose in the inhaled air. Active particles must be dispersed in such a way that they can reach the lungs and remain there [12]. A dry powder formulation consists of a relatively coarse carrier with good flowability that is coated with a small amount of fine, cohesive, and poorly flowable drug particles. The typical median particle size for a coarse carrier is on the order of 50–100 µm and that for small drug particles is on the order of 1–5 µm. Options for the processing of a DPI device are illustrated in Figure 1. The choice for a carrier-based DPI depends on the particle size reduction or engineered API properties. In the case of particle size reduction by micronization, most formulations require a carrier; however, a carrier-free formulation might be possible. In the case of API particle engineering, the choice of carrier is not excluded; however, in most cases, it is not required when proper engineering is performed. However, carrier-free formulations are beyond the scope of this review. The manner in which the powder is metered depends on the choice of device. For example, blisters and capsules contain a single dose that must be opened/broken before inhalation by piercing. For reservoir devices, a single dose must be metered from the reservoir into the device. Upon inhalation, a single dose of powder is dispersed in the airflow generated by respiratory action. During air dispersion, drug particles are released from the coarse carrier for pulmonary delivery.

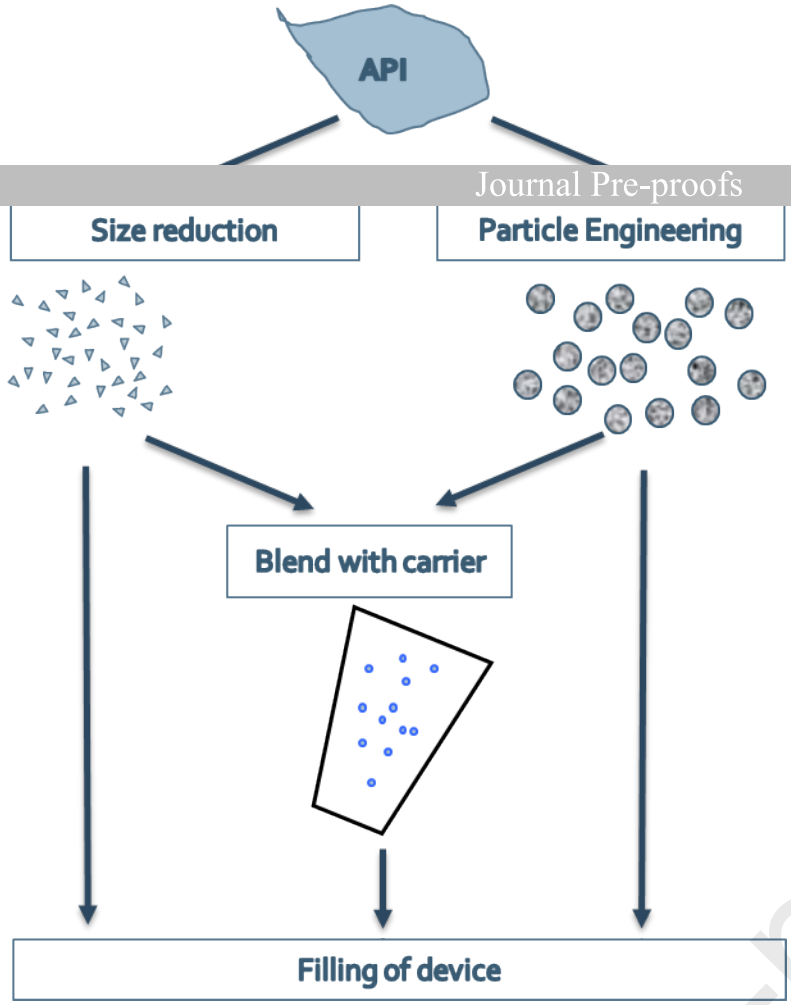


Figure 1. Schematic representation of the steps required in a DPI formulation process, starting from the API, employing size reduction or particle engineering, and ultimately to the filling of the device with or without the addition of a carrier.

1.2. Overview of recent commercial DPI devices

Currently, many commercial carrier-based dry powder formulations are available on the market from several drug manufacturing suppliers. Examples of these can be found in several review papers [2,13–15]. Table 1 shows a selection of DPI devices that were recently launched in the market, including an example of a lactose carrier-free medical device. This overview demonstrates that the vast majority of DPI products are based on lactose as the carrier excipient.

Table 1. Selection of recently launched DPI devices

Type of	Manufacturer	Device name	Excipients	Launched	Medical product
Capsule	Novartis	BreezHaler® [16]	Lactose monohydrate, magnesium stearate	2011	Atectura® Enerzair® Onbrez® Seebri® Ultibro®
Capsule	Glenmark	MRX003-R®	Lactose monohydrate	2021	Tiogiva®
Reservoir	AstraZeneca	Genuair [17]	Lactose monohydrate	2014	Duaklir® Eklira®
Reservoir	Chiesi	NEXThaler® [18]	Lactose monohydrate, magnesium stearate	2017	Foster® Trimbow®
Reservoir	Orion	Easyhaler® [19]	Lactose monohydrate	2018	Budesonide Budesonide /formoterol Formoterol Salfuler
Blister	Sandoz	Forspiro® [20]	Lactose monohydrate	2014	AirFluSal® AirBuFo®
Blister	GSK	Ellipta® [21]	Lactose monohydrate; magnesium stearate	2017	Relvar® Incruse® Anoro® Trelegy® Arnuity®
Blister	Mylan/Viatris	Wixela Inhub® [22]	Lactose monohydrate	2019	Generic version of Advair Diskus
Blister	Hikma	Fluticasone propionate and salmeterol xinafoate	Lactose monohydrate	2021	Generic version of Advair Diskus
Blister	TEVA	Fluticasone propionate and salmeterol xinafoate	Lactose monohydrate	2021	Generic version of Advair Diskus
Blister	Mannkind	Afrezza inhaler [23]	fumaryl diketopiperazine Polysorbate 80	2014	Afrezza®

As illustrated in Table 1, there are several manufacturers of DPI drug products, both from originators such as GSK, AstraZeneca, Novartis, and Chiesi, and generic companies such as Hikma, Mylan, and TEVA that provide generic versions of, for instance, Advair Diskus® formulations. The originators have several formulations for DPI and continue to launch new formulations on existing platforms. All commercial formulations use lactose monohydrate or a combination of lactose monohydrate and

magnesium stearate as the excipients. The launch of new generic products will erode the existing market share of originator products. Most DPI devices are carrier-based with lactose as the excipient of choice. The Afrezza Mannkind inhaler for insulin delivery is one of the few examples of a carrier-

2. Design of DPI formulations

Several aspects play a role in the development of dry powder inhaler devices. Schoubben et al. [24] used the term 'Ménage à trois' specifically to emphasize the intertwined relationship between powder, capsule, and device in a dry powder inhaler. They created a formulation of capreomycin for the treatment of tuberculosis. The formulation was optimized by designing the excipients and the production process of capreomycin. With the choice of the proper device and the right capsule, optimal results were obtained. In an "expert opinion review" by de Boer et al. [25], the same interaction of several design aspects led to advice for a more holistic approach. A proper design of a DPI formulation with optimal functionality requires the design of the carrier and API in relation to the chosen device. Historically, DPI devices have been designed for low-dose drugs for lung-related diseases, such as asthma and COPD [25]. This remains an important area for DPIs, but new and different dosage forms for new therapeutic areas currently require higher doses of active ingredients. This will have an impact on future formulations and developments. This review will focus on research on optimized carrier-based dry powder inhaler systems and will show which strategies are chosen based on several aspects of the formulation, with a holistic view of the formulation, including devices. Although we will mention high-dose formulations and carrier-free formulations, the focus will be on lactose carrier-based formulations.

2.1. Design of the carrier

Almost all marketed dry powder inhalers contain carrier-based formulations. This implies that the active ingredient is combined with an inert carrier material, which in many cases, is α-lactose monohydrate (generally designated as lactose). Lactose is one of the few FDA-approved excipients for inhaled therapy and has a long and safe history in the development of dry powder inhalers [11]. Even for patients with lactose intolerance, lactose is safe to use as an excipient for inhalation, as the amount of lactose inhaled is very low (< 50 mg) [26]. Hypersensitivity to bovine milk proteins is rare but has been reported [27]. In such cases, lactose, despite its high purity, cannot be used as an excipient during inhalation, and alternative formulations should be used [28]. Therefore, most of the understanding of the carrier role in formulations is based on studies on lactose and, more specifically, α-lactose

monohydrate [29]. There are many different polymorphic forms and morphologies of lactose, such as anhydrous or β-lactose, spray-dried, and granulated lactose [30]. Potentially, all available forms can be used as carriers in DPI; however, α-lactose monohydrate is the most dominant form of lactose used

carrier-based DPI have built on that successful platform.

The interaction, or adhesion, between the carrier and API particles plays an vital role in carrier DPI formulation for filling and deagglomeration during inhalation. Theories of several mechanisms have been developed to describe these interactions [33–37]. Physical interactions, such as van der Waals forces, form the basis of adhesion; however, the particle size distribution (PSD) of various powder components also plays an important role. Owing to the accessibility of APIs to the lungs, they are generally micronized to meet the required aerodynamic particle size to reach the deep lungs. Carriers with relatively large particle sizes are used to reduce particle cohesion and improve the powder flow of cohesive and poor-flowing APIs. This results in a mixture in which the fine particles of the API are distributed over the surface of the larger carrier. This is described as an ordered or adhesive mixture [38]. The total number of fine API particles in relation to the surface area of the carrier also plays a role. A few small API particles will preferentially adhere to strong binding sites at the surface, referred to as the 'active sites theory' [34]. At higher API doses, other parts of the carrier surface are covered, followed by the formation of multilayers of small API particles on the carrier surface at even higher doses, depending on the cohesion and adhesion forces of the particles. Fluidization and agglomeration [39] mechanisms play a dominant role in the functionality of powder inhaler. Optimization of the carrier for DPI formulations is centered around particle–particle interactions, the relative amount of fine particles in relation to the available carrier surface area, blending strategy, and design of the device. There are several ways in which all aspects, either individually or in combination, can be exploited to achieve optimal DPI formulations.

The relative surface area and associated morphology of the active ingredient versus the carrier material are also important to the efficacy of dry powder inhalers. The PSD is one of the most important parameters with regard to the specific surface area of a powder. Particle size is a multidimensional parameter, and there is no single answer to the effect of the PSD on the functionality of a DPI device. There are many ways to define the particle size, which are related to the way it is measured [40]. The geometrical PSD in a DPI is generally measured using laser diffraction [41]. A powder is dispersed in a suitable medium, in many cases, air, and passed by a laser beam, resulting in the diffraction of that beam by the particles. The geometric PSD is calculated based on the diffraction pattern of the laser beam. To reach deeper lungs, that is, the alveolar region, the aerodynamic particle size of the API is important. This size is different than the geometrical PSD, which describes the physical

size of the particles, whereby the envelope density of the particle does not play a role. Here, the envelope density, also designated the effective particle density, is defined as the mass of the particle divided by its volume, including pores and cavities. The aerodynamic particle size is a function of the

$$d_a = d_g\sqrt{\frac{\rho_e}{\lambda\rho_s}}, \quad (1)$$

where d_a is the aerodynamic particle diameter, d_g is the geometrical particle diameter, ρ_s = 1 g cm^{-3}, ρ_e is the effective or envelope particle density, and λ is the dynamic shape factor [42]. The aerodynamic particle size is smaller if the particle has a lower density. The aerodynamic PSD can be measured by a cascade impactor, such as a Next-Generation Impactor (NGI) [40]. Most relevant studies, however, have focused on the geometrical PSD, as it is easier to measure. In many cases, the active ingredient is a milled crystalline powder with a particle envelope density similar to that of the unmilled powder. In these cases, the geometric PSD is a good predictor of the aerodynamic PSD; however, for registration purposes, aerodynamic PSD is required. Furthermore, the milling process affects the dynamic shape factor λ, which is difficult to determine experimentally. Therefore, aerodynamic particle size is the most relevant particle size for inhalable APIs. The carrier material does not need to reach the lungs at all; therefore, the aerodynamic PSD of the carrier is, in most cases, irrelevant. Coarse lactose particles are deposited in the mouth and throat, swallowed, and typically are not inhaled.

The functionality of DPI devices is determined by measuring the aerodynamic particle size of the formulation, for example, a cascade impactor, such as an NGI. The performance of a DPI is often expressed as the fraction of API with the correct aerodynamic particle size, expressed as the fine-particle dose (FPD, the absolute amount of API) or fine particle fraction (FPF, the amount of API relative to the emitted or loaded dose) [4]. An upper aerodynamic diameter of 5 µm is generally used as the cutoff size for calculating FPD and FPF.

2.1.1. Carrier modifications

Excipients such as lactose are obtained by large-scale industrial processes [30,43] that produce crystalline powders with relatively large particle size. The most basic PSD modifications can be achieved by downstream processes such as milling and sieving, which result in the availability of many commercial grades of lactose with different PSD from various manufacturers [30]. Figure 2 provides a schematic representation of these processes [44] that start with a coarse grade of pharmaceutical lactose with a typical Tomahawk shape [30]. Comminution processes, such as milling and

micronization, break the original particles into smaller ones. Classification processes, such as sieving and air classification, split a powder into two or more size classes. Blending processes bring two size classes, and combining these processes can provide unlimited combinations of PSDs.

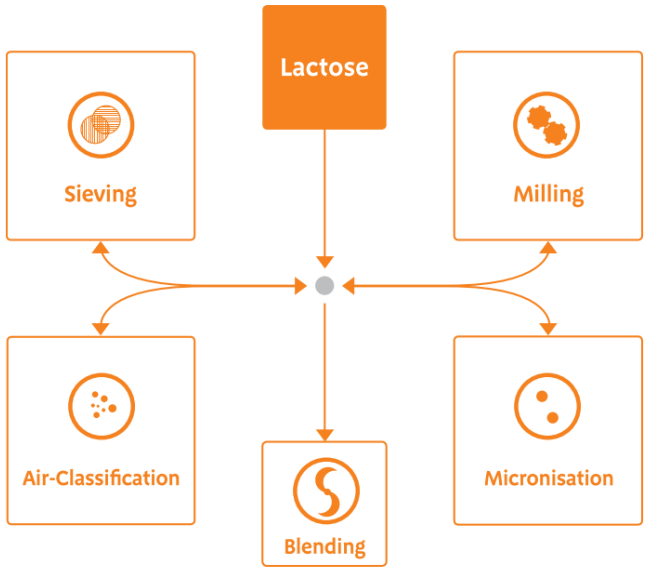


Figure 2. Industrial unit operations that are used to define a specific particle size distribution for lactose [44]

In the early stages of DPI devices, it was recognized that the PSD of the carrier is related to its functionality [45–48]. It was concluded that the presence of fine lactose particles has a strong positive effect on the performance of the DPI blends [49]. With too few lactose fines present, the detachment of the active ingredient from the carrier was ineffective, resulting in a significant amount of API fines that remained attached to the surface at preferential locations, known as active sites [50]. Sun et al. [51] investigated the effect of the fine lactose ratio in a blend on DPI powder properties and performance. Salbutamol sulfate was used as the active ingredient, in combination with coarse- and fine-grade lactose. A positive correlation was found between the device functionality, characterized by the FPF, and the lactose fine content. Adding more fines did increase the FPF but not linearly, and above a maximum value of 15% w/w of fines, no further improvement in FPF was found. This is in line with previous work, where different dominant mechanisms were described to be responsible for the effect of fines in enhancing the FPF [39,50]. Below a fine lactose content of 3% w/w, adhesion between the carrier and API played a dominant role. This is consistent with active site theory, in which lactose fines populate the active sites on the coarse lactose carrier, resulting in a weaker adhesion between large lactose carrier particles and API. Above a fine lactose concentration of 3% w/w, adhesion to active sites was no longer dominant. The dominant mechanisms were governed by cohesion forces at higher concentrations, that is, the interactions between the particles of the active ingredient. These

interactions were characterized by the fluidization mechanism at a medium fine concentration between 3%–10% w/w, whereas the aggregate mechanism dominated at a high fine concentration above 10% w/w. In the fluidization mechanism, the fluidization of the powder exhibits a higher

Agglomeration theory states that the fines form multilayers and aggregates at the surface of the coarse carrier, which are more easily detached from the surface. Both these mechanisms improve the functionality of the formulation [33,35].

Powder flow analysis is commonly used to calculate the ideal amount of lactose fines in DPI formulations. In a study by Hertel et al. [52], the amount of fines in a DPI formulation varied with the two types of coarse lactose. The FPF was determined in two types of inhalers: Novolizer®, a reservoir device, and Cyclohaler®, a capsule device. The powder flow and rheology of the blends were determined using a powder rheometer [53]. It was found that for both DPI devices with low fine content, there was a relatively strong increase in FPF and flow as the fine content increased. The improvement in FPF is explained by active sites theory, in which active sites become saturated with fines at low concentrations. This effect plateaus or decreases above a certain level of fines, which could be explained by other mechanisms such as agglomeration and fluidization theories [52].

In addition to the role of fines in aerosolization, Shalash et al. [54–56] investigated combinations of coarse and micronized lactose in the mixing process of DPI formulations. The micronized lactose particles promoted the breakup of cohesive active ingredient agglomerates, which is an additional positive effect of lactose fines on the overall performance. The influence of carrier microstructure on the DPI performance of fluticasone propionate was investigated by Shalash et al. [55]. The microstructural properties of several different carriers were investigated, demonstrating that the microporosity and air permeability of the carriers are key factors in their functionality. Three classes of pores were defined (Figure 3): nanopores (0.007 – 1 µm), micropores (1 – 8.06 µm), both exhibiting a positive effect on functionality, and macropores (8.06 – 150 µm), which have a negative effect. API particles exhibit weak adhesion to surfaces with nanopores, which results in improved performance. Micropores play a role in effective mixing, thereby improving performance. Macropores provide areas where API particles can bind strongly and are protected against fluidization during inhalation events, resulting in poor performance. The addition of fine excipient material increased the microporosity and reduced the air permeability of the blends, both of which had a positive effect on the performance. This is recognized as a new mechanism characterizing the effect of fines on DPI performance.

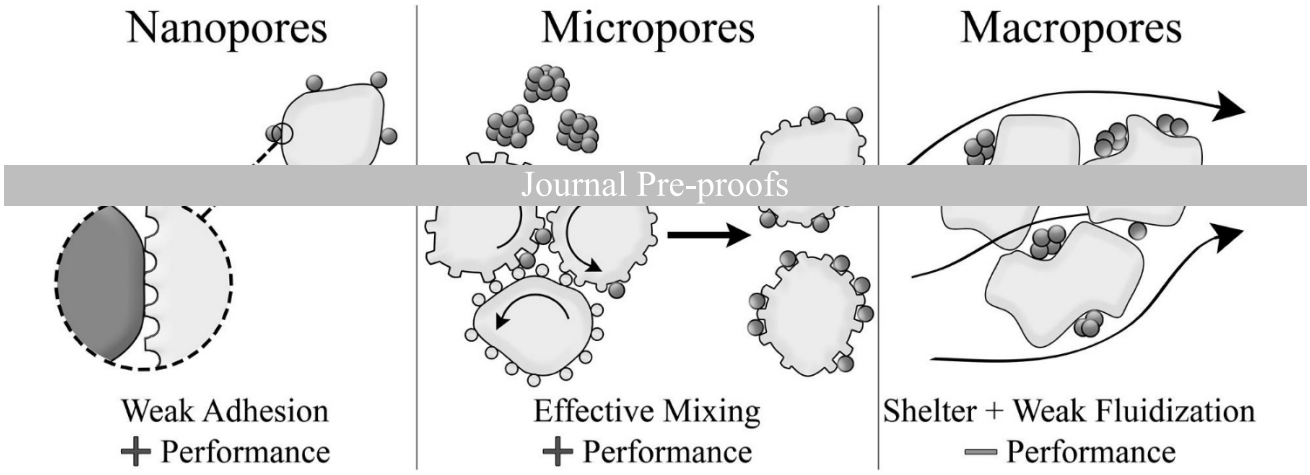


Figure 3. Shalash et al [55] *defined three classes of pores on the carrier and investigated their influence on performance in DPI mixtures. The presence of nanopores results in weak adhesion between carrier and API, and the presence of micropores improves the mixing. Both have a positive effect on performance. Macropores form shelters for API particles and have a negative effect on performance.*

The air permeability of DPI formulations has been investigated in various studies [54,56], which conclude that an optimum value exists. A permeability that is too low or too high results in decreased functionality. This is similar to fluidization theory, in which fines are used to enhance functionality, and also shows that this enhancement is limited to an optimum amount of fines in the blend [36]. This can be regarded as a rule of thumb, as many more parameters, such as carrier size and porosity, also play a role.

Mehta et al. [57] studied the influence of lactose fines on the *in vitro* aerosol performance of a DPI formulation containing fluticasone propionate. They used coarse-grade lactose with a finely milled grade of 0–35% w/w. An optimum level of 20% w/w fines in the blends was found. Consistent with other studies [51], the optimum is not constant, illustrating that optimization is required for each specific DPI. The loading capacity of the lactose carrier was investigated by loading the carrier with a micronized grade of lactose as the API model [58]. The maximum loading that could be reached depended on the particle size and surface roughness of the API and carrier combination chosen. Additionally, the dependency on the mixing process was found to be minor, and surface modifications have a much larger effect on the aerosolization properties.

Besides milled and sieved grades, the role of other grades of lactose, such as granulated lactose [59,60] and anhydrous lactose [61], has also been studied in DPI. The size of granulated lactose carriers [59] is relatively large compared to the standard size of coarse lactose carriers that can be obtained by milling and/or sieving. A larger lactose granule size results in more efficient formulations in terms of functionality. A recent study by Du et al. [60] showed that this behavior is not only dependent on the lactose particle size but is also related to the specific API and API loading. At relatively low loading, the smallest carrier size performed better, whereas at increased loading, the larger particle size performed

best. Spherical lactose particles were prepared by spray-drying a lactose solution [62]. The amorphous lactose generated by the spray-drying process is sensitive to humidity; therefore, the relative humidity (RH) should remain below 30% for this carrier. Different polymorphic forms of crystalline α-lactose

enhanced the functionality of the salbutamol sulfate formulation, as compared with the formulation with standard α-lactose monohydrate polymorph. This difference was attributed to the different adhesion properties of the types of lactose, which led to different adhesive interactions with the API.

As is shown in this paragraph, much research has been conducted to understand the impact that particle size of API and lactose carriers play in inhalation efficiency. Several models have been developed to generate an understanding of the relation between carrier and API to predict performance. However, these models have limitations. Each model is only, or partially, valid under certain parameters, pertaining to characteristics such as the API type, loading, type of device, and size and shape of the carrier. In conclusion, despite these models and rules of thumb, each new formulation requires a thorough development approach, in which the API and carrier are developed together to achieve optimal performance.

2.1.2. Surface modifications

All theories on powder blending and aerosolization indicate that the surface area of the carrier plays an important role. As described previously, fines can be used to modify this surface, and several theories have been developed on the role of fines in the blending and aerosolization processes. Dickhoff et al. [65] modified the lactose surface by submerging the carrier particles in a mixture of ethanol and water. The size and shape of the carrier particles were not altered by this treatment. However, the specific surface area decreased significantly, which was attributed to the removal of the lactose fines. This resulted in reduced drug particle detachment caused by the reduced shelter of the API particles against the press-on forces during mixing. Another important aspect is the surface energy of the carrier material [66,67]. The surface energy is strongly associated with active site theory, as these active sites can be regarded as areas of high surface energy. Using finite-concentration inverse gas chromatography [67–70], up to 20% of the surface area of a carrier can be described in terms of the surface energy distribution [68,69]. Ho et al. evaluated the effect of lactose fines on the surface energy of a coarse and fine lactose mixture [69]. Fines increase the surface energy heterogeneity because they have a higher surface energy. In a publication by Bungert et al. [68], the crucial influence of the adhesion properties of fines based on different surface energies was investigated. It was shown that lactose fines with a high-energy surface have strong adhesion with ipratropium bromide (API)

particles. In the agglomeration mechanism, the detachment of fine agglomerates from the surface of a large carrier particle is essential [39]. The higher the adhesion between fines and API, the stronger the agglomerates that form, resulting in enhanced aerodynamic performance.

Young et al. prepared lactose carrier particles with different levels of surface roughness by fusing primary lactose particles of varying sizes [71]. Variations in the surface roughness of the fused carrier particles were found to be related to changes in drug particle adhesion and the resulting drug aerosol performance of the lactose-drug blends. A higher carrier surface roughness resulted in a higher *in vitro* FPF, which could be explained by the reduced contact area between the drug particle and carrier surface with increased surface roughness. This reduction produces a reduced drug–carrier adhesion force, which improves drug aerosolization performance. Therefore, designing lactose carriers with variations in surface roughness could be an effective approach to optimizing aerosolization performance.

For lactose, attempts have been made to convert the surface energy heterogeneity obtained from finite dilution inverse gas chromatography (IGC) into a description of the surface area [72,73]. By applying mathematical techniques, Karde et al. demonstrated that parts of the lactose surface could be described with a specific surface energy [74]. A couple of distinct areas were described in this manner, in which the magnitude of the peak was correlated with the relative area size of the specific energy areas. The specific energy can be modified by processing techniques such as milling and sieving. Greater milling, resulting in finer powders, corresponded to larger high-energy areas on the lactose surface. Sieving also affected the surface energy but on a much smaller basis than milling, mainly owing not to the sieving process itself but rather the higher surface energy spots on the finer fractions.

In a different approach, the surface energy of lactose was determined using atomic force microscopy [75,76]. Here, the work of adhesion between a surface lactose and a small API particle can be measured. By measuring both the work of cohesion (lactose–lactose and API–API) and that of adhesion (lactose–API), the cohesive–adhesive balance (CAB) can be determined [77]. The prediction of performance prediction was found to be more successful with CAB than with IGC. Therefore, the surface area assessed is only a fraction of the total area, whereas in CAB, the real interaction between two particles is measured, which involves a larger surface area.

A machine-learning approach for the surface design of a DPI carrier was proposed [78]. In this approach, 13 surface-related parameters were combined with literature-based DPI functionality data. A detailed analysis of the relationship between the carrier surface variables and the emitted dose (ED) and FPF indicated that carrier surfaces with highly irregular crevices and different orientations are

more suitable for achieving high ED, suggesting that a balance between peaks and valleys on the surface is required for the carrier surface to achieve a satisfactory FPF.

2.1.3. Ternary components

A common approach in DPI formulations is to combine the active ingredient with a carrier that has both coarse and fine grades, e.g., lactose. In many cases, this is referred to as a ternary formulation. However, in this discussion, the ternary components involve the use of a third component that is chemically different from the lactose carrier. A common approach is to use magnesium stearate as the ternary component [79]. There are several reasons for including a third component, such as enhancing the stability of the API, improving the dispersion of the API, decreasing the stickiness of powder to devices, or enhancing the filling efficiency [80]. In 2005, Begat et al. [81] discussed the use of non-lactose ternary components such as leucine, lecithin, and magnesium stearate, which they referred to as 'force controlling agents' (FCAs). Powders were treated with a dry fusion process called mechano-fusion, which involves high shear forces that force the ternary agent to be efficiently dispersed or coated onto the surface of the lactose carrier. The adhesion between salbutamol sulfate and coated lactose was significantly reduced compared with that of uncoated lactose, indicating that drug cohesion forces were dominant in blends that exhibited decreased functionality. Treating salbutamol sulfate with three different FCAs led to a reduction in cohesion forces and increased functionality [81]. Because the FCAs used are hydrophobic, they could also affect the dissolution of the API. However, the dissolution of the treated API was not considered in this study. Currently, many newly developed DPI devices are based on formulations that contain magnesium stearate as an FCA. Recently, an increasing number of DPI devices have been developed using a combination of lactose and magnesium stearate as excipients, even considered by some to be the "industry standard" [79]. Bungert et al. [68,70] investigated the mechano-fusion process for engineering carrier surfaces using magnesium stearate. Pre-blends were made using a gravity blender, and the blends were subjected to either a mechano-fusion process or high-shear blending process. The PSD analysis did not show significant differences between the blending processes. The high-shear process produced superior coating efficiency but similar efficiency in terms of FPF. There are several ways in which an FCA can be introduced. For example, Lau et al. showed the impact of magnesium stearate on aerosolization performance [82] by first preparing a pre-blend of an API (beclomethasone dipropionate), magnesium stearate, and lactose. The blend was subjected to micronization by jet milling. The stability of the blends with magnesium stearate was enhanced compared with that of the blends without magnesium stearate. The effect of varying amounts of magnesium stearate in combination with the mixing intensity on the functionality (FPF) of adhesive and cohesive APIs (with respect to the lactose carrier)

was investigated by Jetzer et al. [83]. Regarding the cohesive API (salmeterol xinafoate), the presence of magnesium stearate had a significant positive effect on the FPF. However, the mixing technique did not have a significant impact on the FPF. Both techniques were equally effective in improving the FPF

did not have a significant effect on FPF. This is attributed to the difference in the interaction of these two APIs with the lactose and magnesium stearate surfaces.

Islam et al. developed several new DPI formulations with new therapeutic compounds based on ternary or quaternary formulations with lactose, magnesium stearate, and L-leucine [84–87]. Carrier-free formulations of meropenem, puerarine, and edoxaban for COVID-19 treatment and glucagon were ineffective, and addition of a coarse type of lactose improved the FPF considerably. The addition of magnesium stearate or L-leucine further improved the FPF and the emitted dosage to some extent [84]. In the case of glucagon [85], it was found that L-leucine was found to be ineffective in improving functionality, owing to a physical interaction between glucagon and L-leucine, preventing efficient deagglomeration. Nicholas et al. coated lactose with magnesium stearate or L-leucine in a high shear blender, followed by the preparation of adhesive mixtures with several APIs and addition of fine lactose [88]. The results showed that fine lactose improved the functionality of the blends for all APIs. Time-of-flight secondary ion mass spectrometry (TOF-SIMS) was used to quantify the surface of the particles in the blends. The arrangement on the surface of the carrier was different for different APIs. Adhesive mixtures of FCA-coated lactose and salbutamol sulfate provided complete coverage of the carrier surface. The carrier surface coverage by the other APIs was only partial, indicating that the surface properties of the API play an important role in the interaction with FCAs. A similar approach involving coating a carrier with magnesium stearate was performed using mannitol as the carrier [89,90]. The same trend was observed for lactose-based ternary formulations in a study by Hertel et al., that is, fines improved the FPF, and the ternary agent improved the inhalable fraction of the blend, although mannitol was less sensitive to this effect than lactose [89,90]. Other ternary components for DPI applications have been reported, such as cyclodextrins [91]; however, in this case, the ternary agent is not used as an FCA or surface coating. Cyclodextrins are important for the bioavailability of APIs in the lungs through solubility enhancement and do not act as carriers. A recent expert opinion review by Park et al. [92] described the necessity of surface modifications in high-dose DPI formulations. In conclusion, in recent years, various new formulations containing ternary agents such as magnesium stearate have been commercially developed. We believe that this trend will continue in the coming years, based on the number of ternary agents containing originator and generic DPIs used in recent years [79] and their benefits regarding chemical and physical stability and functionality.

2.1.4. Morphology engineering of lactose

Techniques used to modify the morphology of carrier particles in high-dose DPI formulations, such as milling, spray, and freeze drying, have been reviewed [92]. Despite the development of these

dominant in the fabrication of high-dose formulations. The preparation of spherical agglomerates of lactose as potential DPI carriers has been reported [93,94]. Spherical agglomerates were prepared by pumping an aqueous lactose solution into an anti-solvent, such as ethanol or acetone. *In vitro* aerosolization showed enhanced functionality over that of sieved lactose. Several other techniques, such as spray-drying, have been employed to engineer alternative forms or morphologies of lactose as carriers in DPI [95–98]. Spray congealing and wet sieving techniques have also been used [95], and aerosolization efficiency is strongly dependent on the topography and structure of the starting material. Highly porous lactose was developed using a single droplet rig [99]. Li et al. prepared formulations of curcumin-containing solid lipid nanoparticles loaded in flower-shaped lactose for inhalation purposes [100].

Spray drying has been exploited in several studies to engineer typical shapes and forms of lactose. For example, an aqueous solution of lactose was spray-dried to obtain amorphous lactose spheres, which were crystallized by treating the formed spheres with boiling ethanol for 10–30 s before filtration and drying [101]. The formed particles exhibited a particular spherical form, in which the size and surface rugosity was dependent on the treatment of the lactose. For example, in a dry powder inhaler with lactose as a carrier, engineered lactose was found to yield better uniformity in the drug content than standard inhalation-grade lactose. In another example by Ke et al., micronized lactose was suspended in isopropyl alcohol and subsequently spray-dried [102], generating a powder with superior stability compared with that from lactose spray-dried from solution, for which a substantial amount of unstable amorphous lactose was formed. Li et al. employed a high-shear crystallization process to engineer lactose particles [103]. A supersaturated lactose solution was highly shear-blended at different speeds for several minutes, with greater shear resulting in smaller particle size. A Rotahaler® was used to measure FPF for the engineered lactose combined with salbutamol sulfate, and three samples and a reference lactose carrier were analyzed. The FPF was on the order of 30%, with the coarsest carrier material exhibiting the highest value, comparable to the reference lactose used; thus, no significant improvement was apparent.

In conclusion, several methods used to engineer lactose carriers for dry powder inhalers have been evaluated. Although promising, these approaches require optimization in the production process of particles and DPI formulation as a whole, impeding the commercialization of these techniques.

Ultimately, most, if not all, of the abovementioned techniques have not yet been successfully implemented in commercial products.

2.1.5. Alternative carriers in dry powder inhalation

As described above, lactose is by far the most commonly used excipient as a carrier material in DPI, and there are potential alternatives available [104,105]. This is because the formulation effectiveness depends on the natural adhesive forces, relative surface area, and blending strategy. Therefore, the same principles that apply to lactose can also be applied to alternative carriers, of which a few recent examples will be discussed here.

Aziz et al. [106] used four different types of excipient carriers: glucose, lactose, mannitol, and trehalose. These were present as relatively coarse milled grade and fine or micronized grade. Micronized oseltamivir phosphate, used in the treatment of viral pneumonia such as COVID-19, was employed as the targeted API. For formulations with trehalose, the aerosolization mechanism of oseltamivir phosphate was governed by the breaking up of agglomerates due to the spacer function of the fine trehalose particles, which facilitates the formulation of this specific drug. Further differences in functionality were minor, with different excipients ultimately producing the same functionality. Sarangi et al. performed discrete element modeling (DEM) on formulations containing either lactose or mannitol [107] and showed that the mechanical properties of the carrier are most important in the aerosolization of the API. Mannitol formulations were found to be more stable under mechanical stress than those of lactose, owing to their higher flexibility or lower Young's modulus. Bettini et al. investigated the effect of different mannitol polymorphs on the DPI performance of several types of APIs [108]. As with lactose as a carrier, a strong correlation between surface properties, which are affected by the crystal type, and performance for the polymorphs was found. A review by Zillen et al. [109] discussed the use of various excipients that could potentially be used in DPI. Their main conclusion is that there is great promise for DPI; however, the safety of many alternative carriers is still unknown and would require extensive (clinical) research before these excipients can be used to administer drugs to the lungs.

2.2. Interaction of the carrier-based formulation with device

Dry powder inhaler devices can be roughly classified as capsule-based, blister-based, and reservoir devices. All these devices interact differently with the powder components during filling, storage, and usage. The lactose carrier provides the required function to the formulation in the filling of the devices (Chapter 4), metering of a dose, and dispersion of the API during inhalation. The device provides the required design for efficient and robust inhalation and the required protection of the formulation to

guarantee the required stability. The powder properties must be aligned with the filling requirements and aerodynamic properties of the device for optimal and robust functionality. In this section, some of the interactions between the powder and device during storage and usage are discussed.

between powder and device. For example, Zhao et al. [110] investigated carrier–API interactions and the effect of lactose shape and device design. The shape of the lactose carriers was suggested to have no significant effect on the API lung deposition patterns. Low actuation flow rates could potentially enhance the overall DPI airway drug delivery efficiency. Using spherical lactose carriers, comparability between a generic DPI and Spiriva Handihaler® was demonstrated for all four actuation flow rates. The quality of aerosolization was found to correlate with the average air-carrier slip velocity, whereas collisions played only a secondary role [111]. Some geometric modifications improved the aerosolization quality, with very little increase in pressure drop across the device. Although these studies provide interesting insights into the design of formulations and devices, modeling still requires the use of many assumptions, and real data are necessary to validate the modeling.

Pinto et al. [112] investigated a pharmacokinetic model to predict the critical parameters of the DPI performance. The PSD, in relation to the type of device, was found to be a critical parameter for performance. For capsule devices, it was estimated that a relatively small carrier with approximately 10% carrier fines was beneficial, whereas in reservoir devices, for which the median particle size was predicted to be the determining factor in performance. The storage of devices by patients is highly important in reservoir devices. After the device was removed from its original sealed package, it was used for many inhalations over an extended period. Radivojev et al. [113] investigated the interaction of moisture with two types of devices, Easyhaler® and Novolizer®. Both budesonide-containing devices were placed at 25 °C and 60% RH, conditions recommended by the International Council for Harmonization (ICH), and at room temperature (22 °C+/-2 °C) at 93–94% RH. Devices containing powders having the lowest particle size and highest amount of fines were the most affected.

2.3. Engineering of API powders

The optimal aerodynamic particle size of the API is often obtained by reducing the geometrical PSD using milling techniques [114,115]. An alternative approach to reducing the aerodynamic PSD is to reduce the envelope density of a particle. To achieve this, specific particle engineering techniques such as spray-drying are required. In many cases, the preparation of active ingredient powders involves excipients to facilitate the formation of composite powders with appropriate aerodynamic

properties and stability [116]. Ke et al. [117] spray-dried APIs from a suspension of lactose in 2-propanol. Inhalable powders were formed, which showed better stability than APIs that were spray-dried from solution alone. It should be noted that co-spray-drying dissolved drugs with suspended

with drugs, whereas other particles are drug-only. The co-spray-drying API with fully dissolved lactose results in the formation of unstable amorphous fractions with loss of functionality upon storage. The amorphization of excipients such as sugars and sugar alcohols, e.g., lactose and mannitol, during spray-drying from solution is a well-known phenomenon and a drawback in the preparation of particles with active ingredients owing to the inherent instability of the amorphous phase. Several strategies can help overcome this problem. Selecting the proper processing conditions is a proven strategy [118]; however, each type of excipient and API requires specific conditions. Crystalline lactose can be achieved by spray-drying a suspension [117]; however, choosing a long residence time with counter-current spray-drying resulted in agglomerates of fine, crystalline lactose [118].

Vancomycin-co-spray-dried powders were prepared in a study by Bahrainian et al. with L-leucin or hydroxypropyl β-cyclodextrin as additives in the spray-drying process, together with bulking agents such as lactose, mannitol, or trehalose [119]. Owing to the presence of dissolved sugars in the spray-dried formulation, the crystallinity changed upon storage, causing unwanted variability in functionality. Phages have recently attracted interest as active ingredients in pulmonary delivery [120–123] for the treatment of cystic fibrosis. The challenge here is to deliver high doses of phages with high activity and stability. Li et al. prepared a phage powder with lactose and leucine as excipients in the spray-drying process [124]. Lactose is present in the amorphous form, and crystallization needs to be prevented by maintaining a sufficiently low RH. Dehghan et al. [125] prepared lactose microparticles containing therapeutic nanoparticles by co-spray-drying a suspension of nanoparticles from a lactose solution. The resulting particles have the right properties to be deposited in the lungs and eventually disintegrate to give back the nanoparticles. Almansour et al. [126] engineered terbinafine inhalable powders by spray-drying with lactose and mannitol as excipients in the solution phase. Both formulations were found to be promising candidates for further development, although the amorphous phase of the excipient required protection. A series of spray-dried inhalable powders were prepared with various carbohydrates, including lactose, as excipients [127]. The engineered particles were characterized according to the shape resulting from spray-drying. The use of a solution provided more reproducible results in terms of aerodynamic properties than did spray-drying from a suspension. However, in all these examples with co-spray-dried lactose, care should be taken, as the excipients are in unstable amorphous form.

In many cases, particle engineering of various active ingredients is successful in the formation of respiratory powders. Additional excipients, such as lactose, are required to facilitate the formation and stability of the particles, resulting in composite particles. Commercial examples of these

of the particles, although it is important to the final formulation, for which it might be used as an additional carrier.

3. Blending of adhesive mixtures for DPI

From the previous section, it is clear that material properties, such as particle size and shape of excipients and API, are crucial parameters for the performance of DPI formulations. Product performance is strongly affected by the particle properties and processing of the particles to make the final DPI. A common processing step in the preparation of DPI formulations is the blending of API with lactose-based carrier particles. The main focus of this section is how this blending process affects DPI formulation and how blending can be used to optimize product performance. A recent comprehensive review of powder mixing for DPI was published by Spahn et al. [129].

3.1. Theory of powder blending for DPI formulations

Powder blending is a critical process for the preparation of DPI formulations. The production of homogeneous adhesive mixtures of drugs and carrier particles is crucial for the performance of a formulation. Interactions between the drug and carrier particles and the resulting aerosolization performance of the adhesive mixtures are strongly dependent on the blending process used. Blending process characteristics such as time, speed, and mixer type, together with the physicochemical properties of the carrier and drug particles, largely determine the properties of the adhesive mixtures obtained. The following section describes the existing theories on adhesive mixtures and active sites, and the resulting effects on blend uniformity and stability. In addition, the different types of powder blenders and process characteristics, and the effects of the blending process on inhalation performance are discussed.

3.1.1. Adhesive mixtures

For the blending DPI formulations containing micronized drug particles and larger carrier particles, the theory for random mixtures [130] cannot be applied because inter-particle interactions are not considered [131]. The blending process results in the adhesion of fine (API) particles to the surface of

the carriers through physical interactions, such as van der Waals, capillary, electrostatic, and mechanical forces [132,133]. Adhesion prevents drug agglomeration and improves drug uniformity within the mixture, as compared with what is theoretically possible for random mixtures [134].

Adhesive mixtures were first reported by Hersey in 1975, who used the term "ordered mixing" to describe the mixing of interacting particulate systems [38]. More recently, the term adhesive mixing has been used, rather than ordered mixing, to describe the blending of small drug particles with larger carrier particles. The advantages of adhesive mixtures over random mixtures include improved blend homogeneity, reduced risk of segregation, and improved powder flow properties. The blending of adhesive mixtures for DPI formulations involves breaking up cohesive drug particle agglomerates and the subsequent adhesion of drug particles to the surface of the carriers. The cohesive interactions between drug particles and the adhesive interactions between the drug and carrier particles were quantified by cohesive adhesive balance (CAB) [76]. Based on this balance, drug particles tend to attach to each other, resulting in drug agglomeration or to the carrier. The dominant interaction depends on the balance between the cohesive and adhesive forces between particles in the mixture. Using this approach, characterizations of the cohesive and adhesive forces of different drug–excipient combinations have been derived [76,135,136]. When the ratio of cohesive force to adhesive force for a specific drug–carrier combination is greater than one, drug particle agglomeration tends to occur during blending. This can not only have a negative effect on blend uniformity and stability but also promote drug dispersion during inhalation [25,135]. When the cohesive adhesive balance is less than one, stronger adherence of drug particles to the carrier surface improves blend stability but reduces the FPF upon inhalation.

The deagglomeration of drug particle agglomerates during blending has been described as a first-order kinetic process [137]. The initial breakage of larger drug agglomerates is rapid and occurs through impact with coarse carrier particles during blending. DEM simulations have indicated that the deagglomeration of fine particles upon impact with carrier particles is dependent on the carrier morphology [138]. The resulting smaller drug agglomerates adhere to the carrier surface. Single drug particles are subsequently deagglomerated by abrasion and erosion caused by the blending process [137]. The tendency of drug particles to adhere to the carrier increases over time during blending [139]. The adhesion strength of particles to a substrate surface has been shown to depend on the force with which the particles are pressed against this surface [140]. During blending, drug particles are compressed onto the surface of the carrier particles by the forces generated by the mixing process. These so-called press-on forces increase the adhesion strength between the drug and carrier because of an increase in the contact area. The magnitude of the press-on forces generated during blending increases with increasing mixing energy [141]. Increasing press-on forces likely shift the CAB toward

drug–carrier adhesion, which lowers the chance of drug detachment from the carrier surface during inhalation [36].

The mechanisms governing the blending of adhesive mixtures have been studied in detail using particle-size analysis [142], in which four different mechanisms have been identified during the blending process, shown schematically in Figure 4. The first mechanism is the distribution of fine particle agglomerates and carrier particles, which can be considered a random mixing process. The second mechanism is the deagglomeration of fine particle agglomerates that results from mechanical collisions during blending. Another mechanism is the adhesion of fine particles or small fine particle agglomerates to the carrier surface. The fourth mechanism involves the redistribution and exchange of fine particles between carrier particles. This also includes the generation of press-on forces, which increase adhesive interactions and improve the stability of the final state of the mixture. The mechanism of fine particle deagglomeration has been shown to be the rate-limiting step for obtaining a uniform adhesive mixture, in which larger agglomerates require prolonged mixing to achieve uniformity [142].

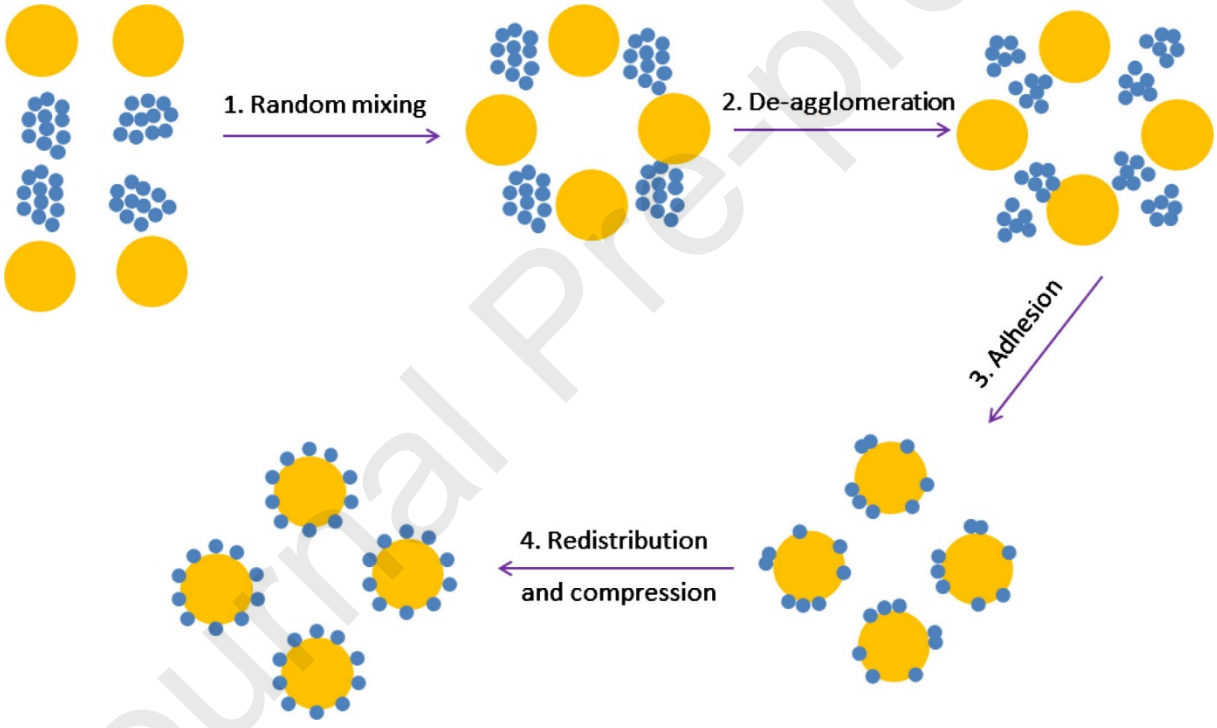


Figure 4. Schematic representation of the mixing mechanisms of adhesive mixtures [142].

3.1.2. Active sites theory in blending

In the previous section, we described the existing dispersion theories on the adhesive mixture in DPI [35]. The most important aspects are the strength of the interaction between the coarse carrier and

formulations, the adhesive forces have a strong influence on the blend stability, and the active sites on the carrier surface play a dominant role. Active sites are defined as areas on the carrier particle surface that are more adhesive than the majority of the carrier surface area [143]. During the blending of adhesive mixtures for DPI, the active sites are more likely to be occupied by drug particles than the carrier sites with lower activity [38]. Drug particles that adhered to these active sites were also less likely to be released from the carrier during dispersion. Based on the release of drug particles from the carrier upon inhalation, an alternative definition of active sites has been proposed, with carrier surface sites that are more likely to retain adhered drug particles during dispersion [144]. According to this alternative definition, the activity of carrier surface sites is dependent not only on the physicochemical properties of the carrier surface but also on the dispersion conditions, blending process of drug and carrier particles, environmental conditions such as RH, and drug particle properties. These variables determine the likelihood of drug particles being either separated from or retained on the carrier surface.

Active sites that are more likely to retain drug particles can be explained in terms of surface irregularities, in which drug particles adhere to multiple contact points, resulting in stronger adhesive interactions [144]. Alternatively, the active sites can also be caused by amorphous regions in the crystal structure of the carrier [145] or by moisture adsorbed to the carrier surface [146]. For example, the separation energy of the drug and carrier particles has been shown to increase when the lactose carrier surface is exposed to a higher RH [147]. Because particles adhered to such active sites are less likely to be released during dispersion, adherence of drug particles to active sites often needs to be avoided. A common approach to achieving this is the addition of fine excipient particles. These fines occupy the active sites of the carrier particles, allowing the drug particles to adhere to weaker binding sites on the carrier surface, with a higher propensity to be released during dispersion. Thus, the addition of fines has been shown to improve the drug product performance of DPI formulations [49,148,149]. At higher fine doses, other mechanisms such as agglomeration, fluidization, and press-on forces play a more dominant role at the surfaces. Such processes are thought to be important to the formation of the blend during mixing and dispersion in an inhalation event. The addition of fine excipient particles has also been shown to promote the deagglomeration of drug particles during blending through the generation of inertial and frictional forces [54]. The addition of lactose fines has a positive effect on the performance of DPI devices [39]; however, it can also have a negative effect

on dispersion performance. The addition of fines has been proposed to increase the effectiveness of press-on forces generated during blending, resulting in stronger adhesion between the drug and carrier [35]. Furthermore, the added fines can result in the formation of fine particle networks on the

Therefore, to prevent the adhesion of drug particles to the active sites, multiple mechanisms must be simultaneously considered when adding fines.

3.1.3. Blend uniformity and stability

For any powder blending process, blend uniformity is an important indicator of efficient blending. In addition, for the blending of adhesive mixtures of drug and carrier particles, homogeneous distribution of drug particles over the carrier surface is an important factor. In addition, the stability of the blend upon further processing and efficient separation of the drug and carrier particles upon inhalation are key factors in the preparation of adhesive mixtures [37]. As discussed in Section 3.1.1, the cohesive adhesive balance of the drug and carrier particles has a large effect on blend uniformity and stability [76]. If the adhesive forces between the drug and carrier particles exceed the cohesive forces between the drug particles, a stable and uniform adhesive mixture is expected. However, if cohesive forces are dominant, detachment of drug particles from the carrier surface and agglomeration of detached drug particles will reduce blend uniformity.

The homogeneity of an ideal adhesive mixture is greater than that of a random mixture. Therefore, the drug content of an ideal adhesive mixture does not vary significantly among different doses [150]. However, in practice, the heterogeneity of adhesive DPI mixtures is much greater than that predicted for an ideal ordered mixture [151]. This can be attributed to the tendency of cohesive drug particles to agglomerate. Furthermore, the distribution of drug particles over the carrier surface is not consistent, preventing the formation of an ideal ordered mixture. Particle size of a drug has been shown to be an important parameter that determines the uniformity of adhesive mixtures [150]. When the drug particle size is sufficiently smaller than the size of the carrier, a higher degree of homogeneity is obtained than that for a theoretical random mixture. Decreasing the particle size of the drug increases the statistical probability of finding a sufficient number of drug particles on each carrier particle, thereby improving blend uniformity [150].

A recent study by Pinto et al. showed that both particle size and the method of processing drug particles affect the blend uniformity of adhesive mixtures for DPI [152]. Both jet-milled and spray-dried particles of salbutamol sulfate with different morphologies were blended with lactose carrier particles at drug loads of 1% and 10% w/w. The adhesive mixtures of jet-milled drug particles with

lactose carriers showed good blend uniformity at both drug loadings tested. This high degree of homogeneity is related to the homogeneous distribution of the milled drug particles on the surface of the carrier particles. At a drug loading of 10% w/w, the presence of drug agglomerates resulted in a

particles with lactose showed poor blend homogeneity, especially at high drug loadings. The spherical spray-dried particles showed a tendency to adhere to irregular areas (active sites) of the carrier particles, resulting in a more heterogeneous distribution of drug particles over the carrier surface and the presence of more unattached drug agglomerates [152]. Thus, morphology, as well as size, of the drug particles strongly affects the blend uniformity of adhesive mixtures.

Using granulated lactose as a carrier, Du et al. showed that the particle size of the carrier also affects the blend uniformity of the adhesive mixtures for DPI [59]. Increasing the size of lactose carrier particles results in reduced blend uniformity. This was explained by the lower surface area of the larger carrier particles, which results in fewer particle–particle collisions during blending and, thereby, a lower adhesion strength between the drug and carrier particles. Drug loading also affects blend uniformity for blends of granulated lactose carriers with salbutamol sulfate or rifampicin drug particles [60]. Increasing drug loading generally has a negative effect on blend uniformity, as the drug loading exceeds the available capacity of the cavities of granular lactose carriers. Therefore, especially at higher drug loadings, blend uniformity of adhesive mixtures can become an issue. The surface roughness of lactose carrier particles has also been shown to affect blend uniformity, whereby carriers with a smoother surface form a less uniform blend with drug particles [153]. A smoother carrier surface results in a lower number of contact points for the adhered drug particles, resulting in weaker adhesive interactions and, thus, reduced blend uniformity.

The stability of the blends of drug and carrier particles within a DPI formulation is critical to ensure the delivery of a consistent drug dose over the defined shelf life. Different processing methods used in the production of drug and carrier particles, such as micronization and spray-drying, introduce amorphous regions on crystalline particles [154]. These amorphous regions recrystallize over time under the influence of water; therefore, the RH during processing and storage can have a large impact on the stability of a DPI blend [155–157]. For example, a strong reduction in the efficiency of a DPI formulation was observed when devices were stored at 75% RH at 40 °C compared to an inhaler stored at 25 °C and 30% RH [158]. The recrystallization of amorphous regions during conditioning at varying RH has been shown to affect the cohesive–adhesive force balance [159]. This can result in the agglomeration of drug particles, which directly affects aerosolization performance. To overcome such stability issues, powders can be conditioned at controlled RH and temperature to allow the conversion

of amorphous to crystalline material prior to blending of the drug and carrier [160]. An extensive review of the physical stability of DPI formulations was recently published by Shetty et al. [161].

The stability of lactose is also been shown to be affected by temperature and RH [162,163]. In β-lactose, epimerization can occur under the influence of moisture, as it has been shown that conversion to α-lactose monohydrate takes place at a high RH of 93% [163]. Meanwhile, α-lactose monohydrate is stable at high RH. If lactose particles contain amorphous material, for example, as a result of milling or spray-drying, lactose stability is strongly affected. Moisture-induced recrystallization of amorphous lactose occurs under milder conditions at much lower RH values [164]. A recent study on the stability of inhalation-grade lactose fines showed that variations in the milling parameters not only affect PSD but also result in differences in amorphous content, cohesivity, and moisture sorption of the lactose fines [165]. Storage of the lactose fines at high RH reduced the amorphous content but also resulted in agglomeration of the fine particles, which reduced the dispersibility of the powders.

3.2. Blending equipment and process settings for the blending of adhesive mixtures

The goal of blending an adhesive mixture for DPI is to produce a homogeneous mixture that is stable during further processing and easily separated into primary particles upon inhalation. The blending efficiency of adhesive mixtures is strongly dependent on the forces applied to the particles in the process. Therefore, the choice of blending process and mixer type can have a significant impact on blend uniformity, stability, and aerosolization performance. The overall performance of a DPI formulation depends on the drug and carrier properties, blending process and equipment, dispersion and deagglomeration within the device, and aerosol characterization. Each operation influences the product performance; nevertheless, the effect of the blending process and equipment has been remarkably overlooked in many studies on adhesive mixtures for DPI [132].

During blending, a combination of inertial, frictional, and shear forces is applied to drug and carrier particles [37]. Inertial forces tend to result in the detachment of drug particles adhered to the carrier particles. However, shear and frictional forces tend to promote the deagglomeration of drug particles and their subsequent adhesion on the carrier surface [166]. Therefore, increasing the shear and frictional forces during blending generally results in increased drug carrier adhesion and improved blend uniformity. Inertial and frictional forces are also responsible for the redistribution of drug particles over the carrier surface. The magnitudes of the inertial, frictional, and shear forces depend on the type of blending equipment and process settings, as well as the physicochemical properties of the drug and carrier particles. The effects of the type of blending process and process settings on the adhesive mixtures are discussed in the following sections.

3.2.1 Types of blending equipment

Solid particles can be mixed via three different mixing mechanisms, with the dominant mechanism depending on the type of blending equipment. Diffusive blending occurs at small length scales, on the

particles, which are distributed over a surface by mixer action, resulting in new particle interactions. Convective blending occurs at larger length scales and is the result of random motions of larger fractions of the powder blend. Groups of particles move with respect to each other, which improves the blend homogeneity at larger length scales. The third mixing mechanism is shear blending, which is related to the powders undergoing convection caused by the velocity gradients created by the blender. Shear blending is caused by high shear strains within a powder bed, which extend the contact area between two groups of particles and, thereby, break up particle agglomerates [167]. Of these three mixing mechanisms, shear blending is the only one that provides sufficient energy to break up the agglomerates of cohesive drug particles in DPI formulations. Therefore, to prepare a homogenous adhesive mixture of drug and carrier particles, a certain degree of shear force must be applied to the particles during blending.

In blending drug–carrier formulations, two different types of blending equipment are typically used. Tumbling blenders, also known as rotary vessels, rotate while the powders tumble around inside. The dominant mixing mechanisms in tumbling blenders are shear and diffusive blending [168]. Examples of tumbling blenders that are commonly used for DPI formulations include Turbula blenders, V-blenders, cylindrical drums, and double cone blenders. The second type of blending equipment includes stationary vessels with internal rotary blades that agitate the powders, also known as impeller mixers. Examples of such stationary blenders include centrifugal blenders, ribbon blenders, and orbiting screw mixers such as Nauta blenders. The dominant mixing mechanism in this type of blender is convection; however, shear mixing also occurs at high rotational speeds. Because a certain amount of shear force is required to break up agglomerated drug particles, both types of blending equipment can be used to prepare adhesive mixtures for DPI.

These two types of blending processes provide different ranges of energy input, which can strongly affect the adhesive interactions between drug and carrier particles. Based on the energy input, a blending process can be qualified as low-shear (< 10 W/kg, e.g., tumbler mixers), medium-shear (10 – 100 W/kg, e.g., impeller mixers), or high-shear (> 100 W/kg, e.g., high-speed paddle mixers). The energy input of the blending process into the powder can be calculated using Equation (2):

$$P(W) = 2\pi\omega T \ , \tag{2}$$

where *P* is the power input of the process in Watt, *ω* is the rotational speed in rps, and *T* is the axial torque for rotation in Nm [37]. An increase in the rotational speed results in higher shear forces applied to the powders. The interactions between drug particles, carrier particles, and adhesive units

shear forces generated during blending results in improved deagglomeration of fine drug particles and stronger adhesive interactions between the drug and the carrier. This improves the homogeneity and stability of DPI blends but reduces drug–carrier detachment upon inhalation, thereby reducing the FPF upon aerosolization.

For tumbling blenders, the energy input generally falls within the low-shear regime of less than 10 W per kg of powder. Impeller mixers apply higher shear forces and fall within the medium- or high-shear regime, depending on the rotational speed and size of the impeller blades. A limited number of studies are available in which these different types of blenders are directly compared for drug–carrier-based DPI formulations. Sebti et al. compared the blending of fluticasone propionate with coarse and fine lactose particles in three types of blending equipment [169]. The adhesive mixtures prepared using a low-shear tumbling mixture showed poor homogeneity and stability, requiring a higher energy input via a planetary or a high-shear impeller mixer to achieve sufficient homogeneity. To obtain sufficient adhesive forces that exceed the cohesive forces between drug particles, the use of more powerful shear mixers is required [169]. In a different study by Clarke et al., blends of nedocromil sodium trihydrate (40% w/w) and lactose (60% w/w) were prepared using low-shear tumbler blending, medium-shear hand blending, and high-shear impeller blending [170]. The medium- and high-shear blending methods were found to provide better blend homogeneity than the low-shear tumbling method. The blends produced by the high-shear blender also showed significantly better FPF than the other blending methods. This was attributed to the higher degree of drug deagglomeration in the high-shear method. Owing to the very high drug loading in this particular case, high-shear blending was required to obtain sufficient deagglomeration of the cohesive drug particles [170].

In a more recent study by Benassi et al., low-shear tumbler blending and high-shear blending were compared for a combination of coarse lactose carrier particles and micronized lactose particles [58]. Increasing the shear applied in the blending process resulted in a more effective deagglomeration of fines but did not increase the amount of fines adhered to the surface of the carrier particles. This was explained by assuming that higher shear forces promote shearing motion between carrier particles, which favors the detachment of fines [53]. In another study by Sarkar et al., the blending of the carrier lactose and fine lactose was systematically investigated in a low-shear double-cone blender and a high-shear propeller blender [171]. The high-shear process resulted in issues with the wall adhesion of fines and abrasion of carrier particles. However, the fines and carriers in these studies were identical

in terms of chemical composition (both lactose), which means that the cohesive forces between the lactose fines and the adhesive forces between the fines and carrier were of comparable magnitudes. Therefore, the capability of fine particle agglomerates to separate into single particles during

An alternative type of blending equipment commonly used for mixing solid materials is continuous powder blenders. In this continuous blending process, the starting materials are continuously fed to the blender at a fixed rate, and the blended material exits the blender at the same mass rate. A continuous blending process has been shown to be advantageous in the blending of a variety of powdered materials, including combinations of drugs and excipient particles [172–174]. However, the use of continuous blending processes is not yet common in the blending of adhesive mixtures for DPIs. This is in sharp contrast to the blending process of formulations for oral solid dosage forms, in which continuous powder blending receives a significantly higher level of attention [175]. The main challenge of a continuous blending process for adhesive mixtures is the consistent dosing of cohesive drug particles, which show very poor flowability and must be dosed accurately in very low quantities. If these challenges can be overcome, for example, by pre-blending the drug with excipients, the adoption of a continuous blending process for DPI formulations could, in some cases, be beneficial in terms of blend homogeneity and stability.

In general, the choice of blending process strongly depends on the shear forces required to obtain a homogeneous and stable mixture. If a low-shear blending process is not capable of achieving drug deagglomeration or sufficient adhesive interactions between the drug and carrier, a medium- or high-shear process merits consideration. If a low-shear blending process results in a homogeneous adhesive mixture, increasing shear forces can shift the CAB toward stronger drug–carrier adhesion. This can result in poor aerosolization performance of the resulting mixture, owing to the low propensity for drug–carrier detachment upon aerosolization. Therefore, the optimal choice of blending equipment largely depends on the balance between the cohesion and adhesion of the components of the DPI formulation to be blended.

3.2.2 Effect of blending process settings

Blending time and blender speed are the most important process settings for the blending of adhesive mixtures in both low- and high-shear blenders. Both time and speed have been shown to influence the adhesion between drug and lactose particles [37]. Increasing the blending time generally improves the uniformity of a mixture of nonsegregating components. However, the opposite may be true for a segregating mixture, and longer blending times can result in reduced uniformity. For adhesive

mixtures in general, it is expected that a longer blending time improves blend uniformity and stability by promoting the deagglomeration of drug particles and adhesion of drug particles to the carrier. For example, in an early study, the adhesion force of micronized salmeterol xinafoate particles to lactose

In a more extensive study on the optimization of mixing conditions for adhesive mixtures, the blending of fine and coarse lactose particles was studied by varying the blending time, speed, and fill level in both a low-shear (double-cone) and a high-shear blender [171]. For both types of blenders, an improvement in blend uniformity was observed with increasing blending time, as shown in Figure 5. The effect of blending time on uniformity was most prominent for the low-shear blender (Figure 5), in which longer times were required to obtain uniform blends. For the high-shear mixer, blend uniformity initially improved upon increasing the blending time but quickly reached a plateau, indicating that a further increase in time did not improve uniformity (Figure 5). The blender speed also had a significant effect on the uniformity of the adhesive lactose mixtures, in which higher speeds improved the blend uniformity for both mixtures. In comparing the blender types, the high-shear mixer formed uniform adhesive mixtures significantly faster than the low-shear mixer. However, both blenders have approximately the same number of rotations, demonstrating that controlling the energy input is key to the formation of adhesive mixtures. In addition to time and speed, the loading configuration also had a significant effect on the blend uniformity for the high-shear mixer. A central loading configuration was associated with a lower RSD, which can be attributed to an initial configuration in which the fines were shielded from the blender walls. For the low-shear mixer, time and speed were the only significant process variables affecting blend uniformity [171].

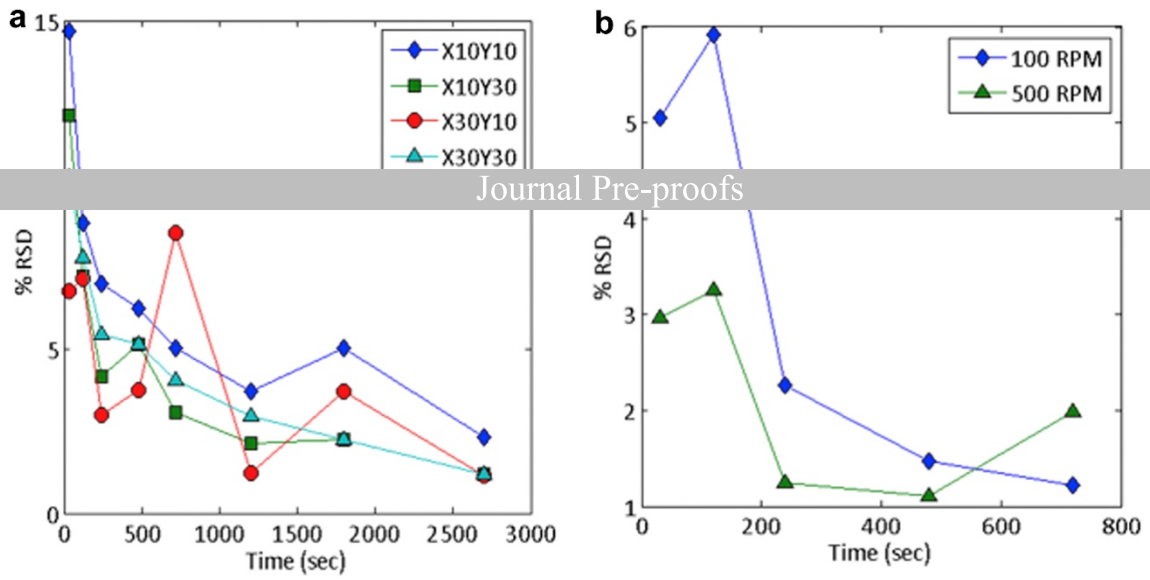


Figure 5. Variation in blend uniformity as a function of blending time for adhesive mixtures of fine and coarse lactose particles in (a) low shear mixer and (b) high shear mixer. For the low shear mixer, the speed was varied around the horizontal (X) and vertical (Y) axis, whereas two different speeds were used for the high shear mixer [171].

Grasmeijer et al. further examined the effects of mixing time on adhesive mixtures for DPI [177]. Blends of lactose carrier particles with two different micronized drugs were prepared in a low-shear Turbula blender at blending times ranging from 0.5 to 780 min. No changes in blend uniformity were observed upon increasing the mixing time, with all blends showing good uniformity, with an RSD below 3%. The drug particle agglomerates were quickly dispersed during blending. Amorphization of drugs upon prolonged mixing may affect the chemical stability of the formulation. In addition, recrystallization at the drug–carrier interface during storage can have a strongly negative effect on drug dispersion behavior [177]. These results show that the mixing time of DPI formulations should be carefully chosen to obtain a balance between the acceptable uniformity and stability of the adhesive mixture.

For adhesive mixtures of lactose with indomethacin, a micronized, poorly water-soluble drug, the extent of drug particle deagglomeration was strongly dependent on blending time and speed in a low-shear Turbula blender [178]. Blending at low speed for short mixing times resulted in incomplete deagglomeration of drug particles. Increasing the blender speed or blending time increased the extent of drug particle deagglomeration, which, in turn, improved the dissolution of poorly soluble drug particles. Increasing the mixing energy by increasing the blending speed or time reduces the size and concentration of drug agglomerates [178]. These results are consistent with particle dynamic simulations of the mixing of cohesive particles in a tumbling blender, which indicates that longer mixing times and higher blender rotation speeds improve the mixing of cohesive particles [179]. In a

different study by Le et al., the effects of mixing time and speed of a tumbling blender were investigated for mixtures of fluticasone propionate with lactose carrier particles [180]. Increasing the blender speed was also found to improve the deagglomeration of API particles, resulting in more

to an unfavorable increase in static electricity during mixing. This effect can be reduced by introducing a rest time during the blending process, which resulted in improved blend homogeneity [180].

The influence of mixing time and speed has also been studied for a high-shear mixing process using budesonide as a model drug in combination with lactose carrier particles and lactose fines [181]. For the high-shear process, no significant effect of the blender rotational speed on blend uniformity was observed, and all blends showed acceptable homogeneity. Increasing the blender speed caused some abrasion of the lactose carrier particles, resulting in the generation of lactose fines during high-shear blending. Previous studies have also shown that a high-shear blending process can affect the PSD of lactose monohydrate particles [182]. In addition, no significant effect of mixing time on blend uniformity was observed for the high shear blender [181]. The short mixing times were sufficient to obtain uniform adhesive mixtures, as shown in Figure 2. However, prolonged mixing time and higher rotational speeds led to lower FPFs of the adhesive mixtures. This is likely due to higher press-on forces acting on the drug particles during high-shear blending. A clear correlation between the energy input into the blend and the reduction in the FPF can be observed. It was, therefore, concluded that shorter mixing times are beneficial for a high-shear mixing process to optimize drug detachment from the carrier [181].

In general, the energy input during the blending process of adhesive mixtures can be controlled by varying both blending speed and time. For a low-shear process, increasing the energy input by using a higher speed or longer blending time is often required to obtain complete deagglomeration of drug particles and acceptable blend uniformity. For a high-shear process, increasing the impeller speed or mixing time often decreases the FPF of the drug, indicating that a higher energy input may increase the adhesive forces between the drug and carrier. Furthermore, increasing the energy input during blending can result in amorphization or abrasion of the drug and carrier particles. Therefore, blending process settings must be carefully chosen to obtain an optimal balance between blend uniformity, stability, and drug detachment upon inhalation.

3.3. Effect of the blending process on drug product performance

For most powder blending operations, the goal of the process is to obtain acceptable blend uniformity. For DPI formulations, however, the blending process is not only used to obtain uniform drug–carrier

distributions but also control the magnitude of adhesive interactions between drug and carrier particles. Therefore, the importance of the blending process for DPI formulations cannot be understated, as it determines both the ability to fill dosing units and the efficiency of drug particle

high degree of uniformity and stability, an increase in the adhesive forces is beneficial. The primary objective of an adhesive mixture for DPI formulation is to achieve a high and consistent FPF. Therefore, the adhesive forces must be strong enough to facilitate the handling of the blend but also weak enough to enable the efficient separation of the drug and carrier particles upon inhalation. Controlling, rather than maximizing, the adhesive forces has become the challenge in the blending process of DPI formulations [132].

The inhalation performance of a DPI formulation is believed to be optimal when the cohesion–adhesion balance ratio of the drug–carrier combination is slightly cohesive [135]. Using combinations of four different micronized drugs with four different carriers, the fine-particle dose was shown to be optimized when the drug–carrier CAB ratio was just above one. When the ratio became more adhesive and the CAB ratio was less than one, the performance of the drug–carrier formulation significantly decreased [135]. However, the blending process of the different drug–carrier combinations in this study did not vary, and all blends were prepared using a low-shear Turbula blender. Whether this relationship between cohesive–adhesive balance and inhalation performance is also applicable for blends prepared by high-shear blending is not clear. The FPF of DPI formulations prepared in a low-shear or high-shear blender has been shown to be comparable, as long as the total number of rotations is equal for both blenders [184]. Increasing the total number of rotations significantly reduces the FPF, owing to an increase in the press-on forces generated during blending. The high-shear blender can be considered advantageous because it achieves similar performance with shorter mixing times compared to the low-shear blender [184].

In a recent study, the effect of increasing the mixing energy in a high-shear blender on inhalation performance was investigated for adhesive mixtures with and without a coating agent [185]. The mixing energy (ME) is defined by Equation 3:

$$ME = 8\pi^3 m f^3 r^2 t, \quad (3)$$

where *m* is the mass of the lactose carrier particle, *f* is rotational frequency of the impeller, *r* is bowl radius of the mixer, and *t* is mixing time. Thus, ME increased linearly with mixing time and the cube of the impeller speed. The effect of increasing ME on FPF was investigated for two different binary drug–carrier combinations [185]. For beclomethasone dipropionate in combination with a fine sieved lactose carrier, increasing ME did not have a significant effect on FPF. However, for budesonide in

combination with a coarser sieved lactose carrier, an increase in ME resulted in an exponential decrease in FPF. The different effects of ME on the FPF of these two formulations were explained by the different sizes of lactose carriers used in these formulations. The larger carrier particles resulted

between the drug and carrier [185]. The vastly different effects of increasing ME on FPF for these two formulations highlight the complexity of the blending process of adhesive mixtures for DPI.

The effects of ME on FPF were further investigated using ternary DPI formulations containing a lactose carrier, drug, and coating agent (leucine or magnesium stearate) [185]. For these ternary formulations, increasing ME resulted in an initial increase in FPF, whereas a further increase in ME caused a decrease in FPF. The optimal ME for each formulation depended on the amounts of drug and coating agent, as shown in Figure 6 for varying ratios of lactose carrier, budesonide, and leucine. The initial increase in the FPF was explained by smearing of the coating agent onto the API particles during blending, which increased their dispersibility. The subsequent decrease in FPF with increasing ME can be explained by the stronger adhesion of the API to the coated carrier surface, owing to the forces generated during the blending process. This decrease in FPF was similar to that observed for the binary formulations. The rate constant of the initial increase in FPF could be reduced by increasing the API loading, whereas the rate constant of the FPF decrease could be reduced by increasing the amount of coating agent [185]. In a similar study using lactose carriers with combinations of beclomethasone dipropionate drug particles and fine lactose particles in a high-shear mixing process, FPF was found to be independent of mixing time for both lactose fines and beclomethasone dipropionate [186]. However, upon the addition of magnesium stearate as a coating agent, the FPF of beclomethasone dipropionate showed an initial increase with mixing time, followed by a decrease for longer mixing times, similar to the behavior shown in Figure 6. The incorporation of drug particles into the carrier surface owing to press-on forces generated during prolonged mixing was suggested as the dominant mechanism for the loss in FPF observed [186].

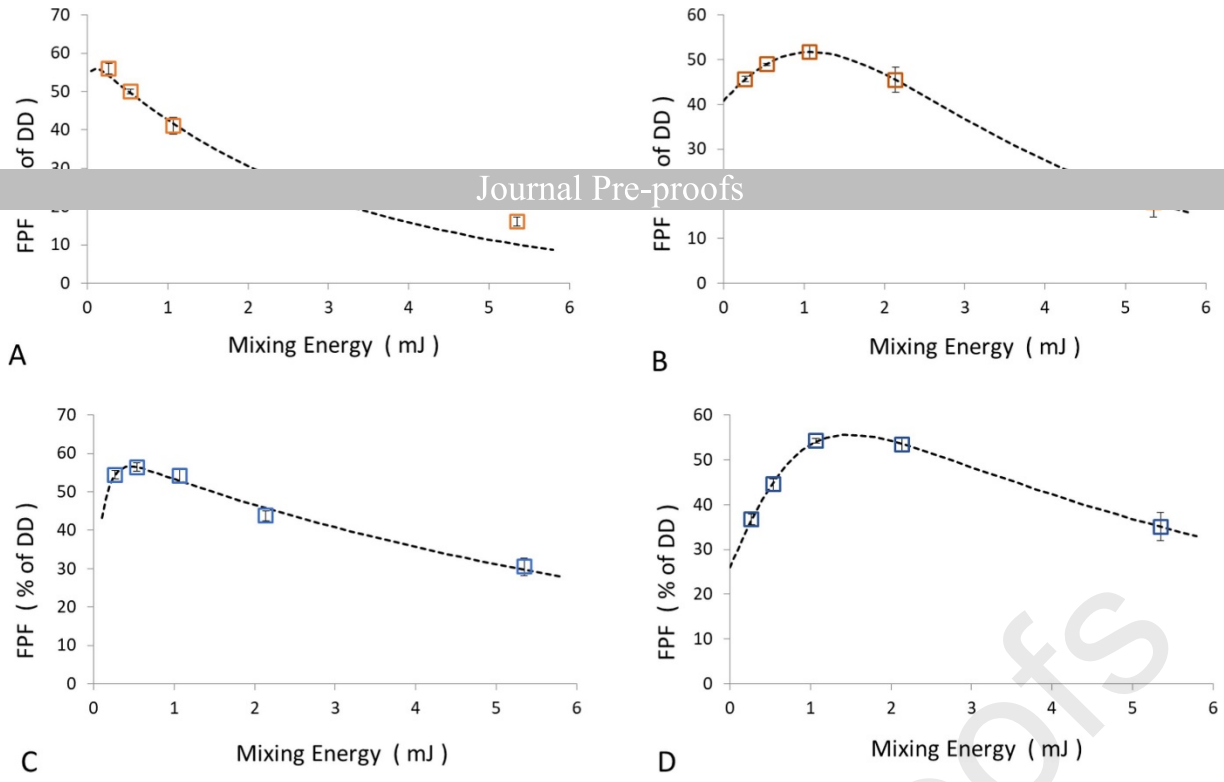


Figure 6. Fine particle fraction (FPF) as a function of mixing energy for ternary DPI formulations containing a coarse-sieved grade of lactose as a carrier and (a) 1% leucine and 1% budesonide, (b) 1% leucine and 5% budesonide, (c) 3% leucine and 1% budesonide, (d) 3% leucine and 5% budesonide [185].

The influence of mixing time on the dispersion performance of adhesive mixtures of lactose and beclomethasone dipropionate has also been investigated in a low-shear Turbula blender [187]. For this low-shear blending process, increasing the mixing time did not significantly affect the FPF of binary lactose–beclomethasone dipropionate blends and ternary mixtures of coarse lactose, fine lactose, and beclomethasone dipropionate. However, the addition of lactose fines significantly increased the FPF of the resulting formulations. The order in which the components of the ternary mixtures were blended was shown to significantly affect the FPF of the drug, in which the addition of fine lactose to either the drug or carrier improved the FPF of the final blend. The significance of the mixing sequence diminished with increasing mixing time, indicating the redistribution of fine lactose and drug particles towards equilibrium during blending. For binary drug–carrier blends, the largest effects of mixing time on drug dispersion were observed within the first hour of mixing in a low-shear blender [177].

The relationship between blending order and drug product performance of ternary DPI formulations containing lactose carrier, lactose fines, and salbutamol sulfate was studied in more detail by Jones et al. [188]. Here, two different blending orders with lactose fines and carrier first or drug and carrier first were prepared at varying blending times and drug concentrations. At the shortest blending time of 15 min, the blending order or drug concentration of FPF did not exhibit a significant effect, likely

because of incomplete deagglomeration of the drug particles after 15 min of low-shear blending. Upon increasing the blending time to 30 min, blends with a low drug dosage showed a higher FPF when lactose fines and carrier were blended first. However, further increase in the blending time to 60 min

higher drug concentrations of 2.5% w/w or more, the blending order showed no significant effect on FPF for any of the three blending times. These seemingly contradictory results are likely related to the formation and breakage of drug–fine agglomerates, a process that is highly dependent on blending time [188]. The interplay between blending time, blending order, and drug concentration highlights the complexity of the effect of the blending process on DPI formulation performance.

A recently developed blend state model was used to link the dispersibility of adhesive mixtures to the concentration of fine particles within the mixture [189–191]. Here, the term "blend state" refers to the spatial distribution of carriers and fine particles in an adhesive mixture. The evolution in the blend state depends on the theoretical surface coverage ratio (SCR), or alternatively, the proportion of fines, of a mixture of a certain combination of carriers and fine particles. Figure 7 shows the bulk density of an adhesive mixture as a function of the blend state with increasing SCR [190]. At a small fraction of fines, corresponding to a low SCR (state 1), fines predominantly gather in the cavities of the carrier particles. This results in an increase in the mass of the ordered units but an unchanged envelope volume, which is reflected by an increase in the bulk density [189]. Upon increasing the SCR, the fines start to adhere to the enveloped surface and form an adhesion layer (state 2), which increases the envelope volume of the ordered units and decreases the bulk density. The second state can be divided into two sub-states (S2a and S2b), depending on the dynamics of the adhesive layer. In S2a, the adhesion layer is relatively stable and insensitive to restructuring because of the forces acting on the blend. In S2b, the growing adhesion layer is responsive to external stresses, and the fines are prone to rearrangement [190]. In the last blend state at a high SCR (state 3), a free fraction of agglomerated fines appears, which is not attached to the carrier. Thus, during the mixing of the carrier and fine particles, an adhesive layer is developed with its thickness and structure depending on the SCR of the blend. The SCR at which the transitions between the different blend states take place is dependent on the size and morphology of the carrier particles and the type of drug [190,191].

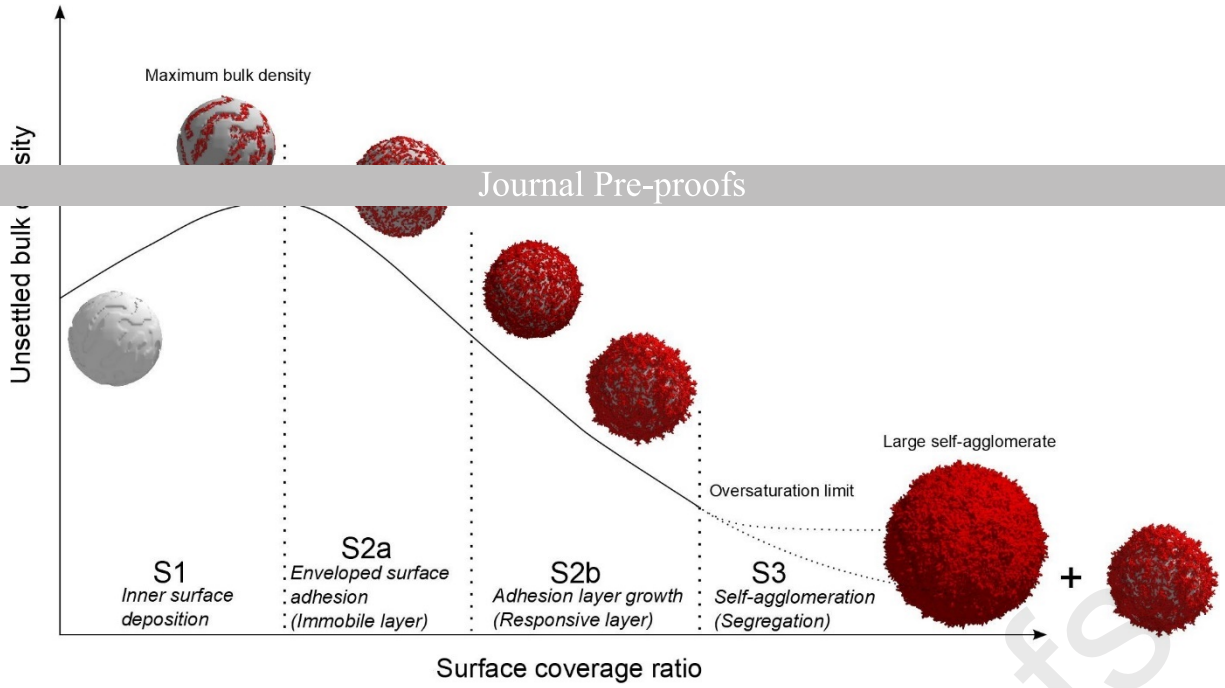


Figure 7. Bulk density as a function of the surface coverage ratio, illustrating the four different blend states in an adhesive mixture, S1, S2a/b, and S3, with increase in the amount of fines according to Rudén et al. [190].

The relationship between the blend state of adhesive mixtures and drug product performance, as assessed by FPF, was investigated for three different APIs in combination with a spray-dried lactose carrier [191]. The adhesive mixtures of all three APIs followed the three main states of the blend state model in terms of structural evolution. The changes observed in FPF with increase in the drug concentration could be explained by the evolution of the blended state. For all three drugs investigated, the FPF increased with increasing drug concentration up to the point in which the FPF reached a plateau, after which a slight decrease was observed. Although the overall trend was similar, the FPF profiles differed, depending on the API, in terms of both the attained FPF maximum and drug concentration at the start of the plateau. The profile describing the FPF as a function of drug concentration can be divided into three regions that are coupled to the blend states of the adhesive mixtures, as shown in Figure 7. In state 1, fine particles are located in open cavities, and a low FPF is obtained. The particles are shielded, strongly adsorbed to the surface cavities, and detached only to a limited degree. When the surface cavities are gradually filled, the particles become less shielded, and detachment becomes easier. Therefore, the FPF strongly increases with drug concentration in this state. In state 2, the FPF continues to increase but at a gradually reduced rate and approaches a plateau. This plateau coincides with the transition from state 2b to state 3. State 3 is characterized by a gradual decrease in FPF owing to the formation of larger drug agglomerates that resist disintegration and dispersion [191].

The blend state model is a potentially useful tool for mapping the mixing properties of drugs in adhesive mixtures. However, this relationship between blend state and drug dispersibility corresponds only to the use of a low-shear Turbula mixer with a mixing time of one hour [189–191]. The

conditions. Therefore, the effect of mixing conditions on the formation of different blend states and the resulting effects on drug dispersion performance require further investigation.

4. Powder filling of dry powder inhalation formulations

As described in Chapter 2, dry powder inhalers can have different designs. DPI devices have been roughly classified as single-dose, pre-metered multidose, and reservoir multidose devices [192]. In a single-dose inhaler, the powder is loaded into a mono-dose compartment, typically a hard capsule. To release the powder upon inhalation, the capsule can be punctured, cut, or opened by detaching its cap. Pre-metered multidose DPIs deliver single doses from pre-metered blisters, disks, or tubes. Reservoir multidose dose devices contain a reservoir with a bulk amount of powder and a mechanism to meter and deliver a single dose upon inhalation [193]. The filling of reservoirs with powders has no additional requirements, as opposed to oral solid dose formulations, and thus will not be reviewed in this chapter. The mass of a single dose or pre-metered dose is generally on the order of milligrams of powder, e.g., 5 mg for Spiriva® (capsule) and 12.5 mg for Seretide® (blister). This very low dosage provides an extra challenge in terms of weight and content uniformity of the dosage in oral solid-dose formulations.

Powder filling into primary packaging is generally the last step in the processing of DPI formulations. Each filling technique has its own requirements in terms of powder density and flowability. Most carrier-based DPI systems contain more than 97% (w/w) lactose. Therefore, lactose grade largely determines the flowability of the formulation. The lactose grades used in a DPI formulation should be carefully selected with reference to the device system and filling platform that will be used in the manufacturing process.

4.1. Filling of capsules

Capsule filling is a well-known technology for oral pharmaceutical formulations. Good-to-poor flowing powders, with a Carr's index [194] ranging from 13.1% to 35.6%, can be successfully filled into capsules

cohesive and show poor flowability. Dosator filling technology is the most traditional filling system used to fill pharmaceutical powders into capsules [196]. The dosator capsule filling process uses a nozzle that penetrates a powder bed of defined height. The powder dosage was metered by the volume of the dosing chamber, which was determined by the dosing chamber length and diameter [197]. The powder was pre-compacted during the penetration of the nozzle into the powder bed and subsequently transferred into capsules. For DPI formulations, the degree of compaction during capsule filling must be minimized to ensure efficient drug delivery to the final product upon inhalation [198].

Faulhammer et al. performed a study on the critical material attributes and process parameters for low-dose capsule filing using dosator filling technology [199]. For noncohesive powders with larger particle sizes and acceptable flow properties, the diameter and dosing chamber length of the dosator and the powder bed height were found to be critical process parameters that affected the fill weight. The bulk and tapped powder densities were critical material attributes, indicating that the dosator filling was volumetric for these powders. The fill weight of the cohesive powders with very fine particles and poor flowability also depended on the dosator diameter, chamber length, and powder bed height. However, for these powders, the dosator filling was not volumetric, and multiple critical material attributes were identified. Powder flowability, wall friction, and bulk density affect the fill weight of cohesive powders [199]. Both cohesive and non-cohesive powders could be filled successfully at low fill weights using dosator systems. Cohesive powders, however, are more challenging to fill, and process control is required for these powders to achieve product specification compliance.

In a similar study using different grades of microcrystalline cellulose, the particle size, air permeability, and compressibility of the powders were found to be critical material attributes for the capsule fill weight [200]. As the fill weight decreased, other material attributes such as wall friction angle, tapped density, and particle morphology proved to be important factors as well. Larger fill weights were more affected by the powder density, whereas low fill weights were predominantly affected by flow and friction characteristics. No correlation was observed between fill weight variability and powder material attributes. Weight variability showed a correlation with process parameters such as filling speed, dosator volume, and compression ratio, which is defined as the ratio of the powder bed height to the dosing chamber length [200].

Stranzinger et al. further explored the effects of material attributes and process parameters on the dosator capsule-filling process [201]. Using three different grades of lactose with large variations in particle size, layer uniformity, capsule fill weight, and weight variability were found to strongly depend

grade LactoHale® 100, the fill weight and weight variability remained constant over time, regardless of the process settings. Furthermore, an increase in the fill weight with increasing filling speed was observed for this coarse lactose grade. For the fine and cohesive lactose grade LactoHale® 220, a strong dependence on the process settings was observed. This more cohesive powder required a lower filling speed at higher dosing chamber volumes for the powder to completely fill the dosator nozzle. Furthermore, a high compression ratio was required owing to the high fill weight variability of the powder over time [201]. These results also confirm that it is more challenging to consistently fill capsules with cohesive powders with low weight variability.

In addition, high fill weight variability can be caused by vibrations of capsule-filling equipment [202]. Increasing the filling speed amplified the vibration intensity, which resulted in powder densification. Owing to this densification, the fill weight was significantly larger at higher capsule-filling speeds. The vibrations at higher filling speeds and subsequent densification also affected powder flowability. Therefore, minimizing the vibrations of the capsule-filling equipment can improve fill weight variability. It is proposed that a quality-by-design (QbD) approach for a DPI capsule filling process should consider the characterization of material attributes under process conditions. Integrating environmental variables such as vibrations into the experimental design space improves the understanding of the critical material attributes that affect the quality of filled capsules [202,203].

The filling of a dosator nozzle moving into a powder bed has also been investigated using DEM simulations [204]. These simulations demonstrate the influence of the powder material attributes on the fill weight. The ratio between the particle and dosator diameters affected the packing of particles within the dosator chamber. In addition, the flowability of the powder significantly affects its filling and compression behavior. Cohesive powders are packed less densely inside the powder bed, which leads to a lower fill weight. In contrast, cohesive powders are compressed more during dosing, and the density inside the dosator chamber increases during the filling process [204]. Simulations showed that non-cohesive and cohesive powders have different filling mechanisms, which explains the different effects of powder bed height on the fill weight of cohesive and non-cohesive powders observed in experimental studies [199].

The effect of the capsule filling process on the *in vitro* FPF has been studied for adhesive mixtures of either lactose or mannitol with salbutamol sulfate [96]. For adhesive mixtures with lactose as a carrier,

it was found that increasing the compression ratio during the filling process resulted in a strong decrease in the FPF. This indicates that a higher compression ratio increases the inter-particulate forces, resulting in the inefficient dispersion of fine particles. For the adhesive mixtures with mannitol

carrier particles was more variable. However, for these mixtures, a decrease in the FPF was observed upon increasing the compression ratio in the filling process. Overall, the DPI formulation with lactose as a carrier and a dosing chamber to powder bed compression ratio of 1:2 showed superior performance in terms of dosing accuracy and *in vitro* FPF [96].

An alternative technology in the filling process of DPI formulations is vacuum-operated systems, in which the powder is sucked into a cavity by vacuum and subsequently ejected into a capsule using pressurized air. Because no mechanical compaction is performed, less lubrication is required, and small doses can be accurately filled [197]. This vacuum-filling technique has been evaluated for the filling of varying lactose monohydrate grades and DPI formulations [205]. The lactose monohydrate-based powders were successfully dosed at the target fill masses of 1 and 5 mg using vacuum-filling technology. Furthermore, the filling behavior of excipients could be related to various aspects of their physical properties. A linear correlation was established between the tapped density and cavity density, which determines the fill weight. In addition, a clear correlation between the variation in fill weight and the PSD of lactose was established, in which finer lactose grades showed reduced filling performance [205]. In a different study using the same vacuum filling technology, vacuum filling was shown to be a suitable method for high-dose DPI formulations [206]. These high-dose formulations were precisely and accurately dosed using a range of different vacuum pressures. The dispersibility of the resulting products was shown to be dependent on the vacuum pressure used during filling [206].

4.2. Filling of Blister strips

Membrane filling systems have been developed and described in the literature for filling lactose-based DPI formulations into blister strips [207]. These blister strips contain multiple pockets that are fully filled with powder up to the rim during membrane filling. The membrane filling system consist of a filling head with a powder hopper and small powder transfer nozzles, which are incorporated into the membrane surface. In vacuum, the air in a blister is evacuated through the membrane, which generates powder flow through the nozzles into the blister cavity until it fills the rim. The particle size and powder flow of the DPI formulation are critical parameters for the filling process of blister strips [80]. Coarse lactose crystals or very cohesive powders can cause clogging of the system, resulting in incomplete filling of inhaled powders. This can be partially overcome by adjusting the internal

diameter of the powder transfer nozzles of the membrane filling system [207]. Pre-compaction is a technology that is used to fill blisters [208,209], and it requires the compacts to be broken before an inhalation action. This is achieved by preconditioning steps that break down the formed compacts into

A study on the filling of formulations containing lactose carriers, lactose fines, and magnesium stearate showed that the compressibility of the powders was a good indicator for the fill weight in the cavity [80]. It was observed that the powder blends with low fine concentrations showed reduced filling consistency. The good flowability of these powders prevented powder compaction inside the nozzle of the membrane filler, resulting in poor filling control. The addition of magnesium stearate further improved the powder flow, making the accurate membrane filling more challenging. It was found that a minimum permeability of the powder blend was required to fill the powders with low variability. Lactose-based blends with poor permeability were either unable to fill or showed higher variability, owing to the good flowability of the powder blend. Therefore, the membrane filling behavior can be optimized by modulating the amount of fine particles in the formulation [210].

5. Future of lactose in inhalation and conclusions

The first DPI device was developed by using lactose monohydrate as the sole excipient. In recent years, there has been a trend towards multi-excipient platforms for DPI [79]. These innovations in DPI carriers have not only allowed the expansion of DPI development options for pharmaceutical companies but, more importantly, have also increased the availability of an increasing range of medicines that are beneficial to patients. Most carrier-based DPI formulations have been developed for diseases related to the lungs and contain formulations with highly active small molecules at low dosages. These traditional boundaries are currently being stretched, with expansion into drug delivery for systemic diseases such as diabetes [211,212], biologics [213] such as monoclonal antibodies [109], proteins [214,215], and liposomes [216–218], as well as into high-dose formulations such as antibiotics for tuberculosis treatment [219–221]. Alternative methods for administering powders to the lungs have also been explored. An example is the merger of MDI and DPI, in which a lactose carrier-based dry powder is administered in tablet form inside an MDI [222–224].

Traditionally, lactose has been the excipient of choice for carrier-based DPI applications. It is widely available, safe, and highly pure. It also has been extensively investigated, and its properties are well

understood. Next, we showed that traditional DPI formulations are complex, and many aspects of the device and formulation need to be taken into consideration. Lactose acts as a bulking agent to improve the powder flowability, which is required for filling, emptying the device, and depositing the API.

few alternatives available; however, they still lack the fundamental understanding that lactose-based formulations have gained in their long history. In addition to the use of traditional milled and sieved lactose as carriers, new morphologies of lactose are being developed, which might assist in the development of future formulations.

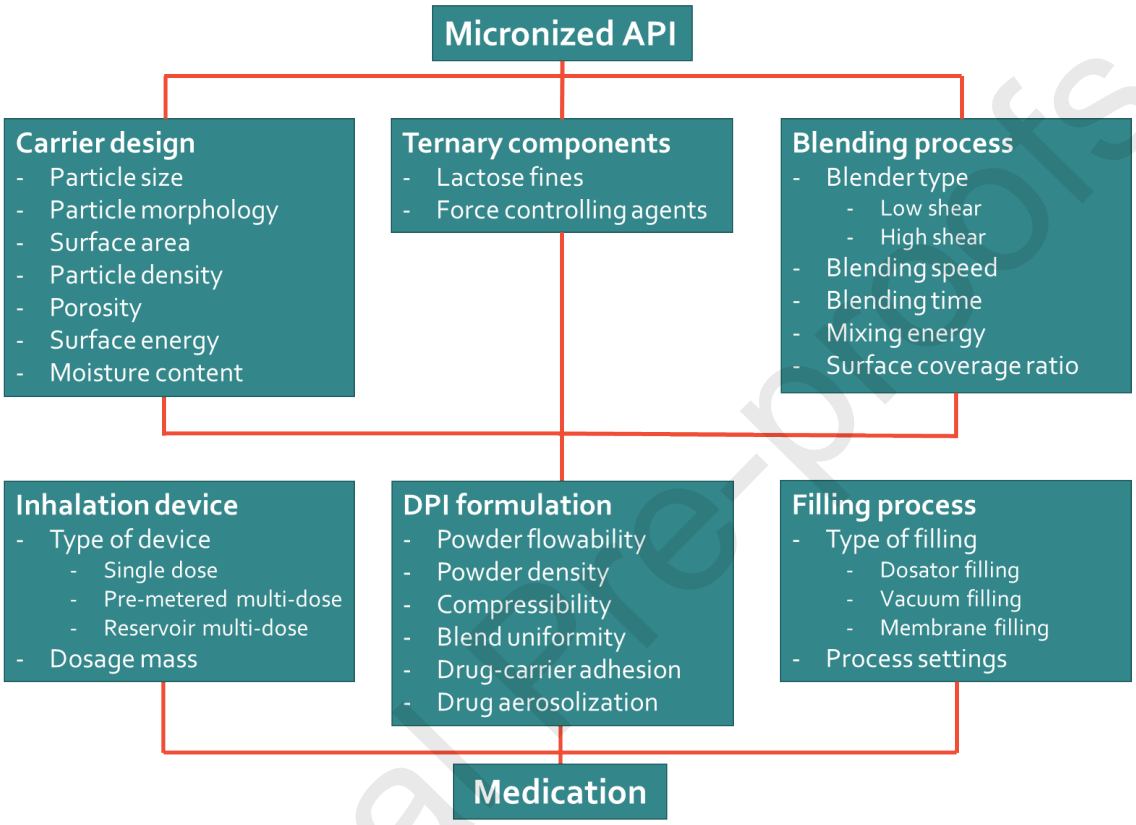


Figure 8. Summary of the major aspects involved in formulating a carrier-based DPI, illustrating a selection of the factors that are relevant for the design of the carrier.

As each dry powder inhaler dosage form is unique, each new, generic, or carrier-based DPI formulation requires proper development. Figure 8 provides a summary of the major aspects to be considered in carrier development during the design of a carrier-based DPI. This may act as a guide for the complex design of stable and effective DPI products. This needs to be performed on a case-by-case basis

because of the complex interactions between the drug, excipient, device, blending process, and required performance.

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