Formulation development of adhesive mixtures for inhalation—A multi-factorial optimization challenge: Part 1

Considerations for APIs, excipients, composition and processing of dry powder formulations

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Synopsis

Dry powder inhalation (DPI) products basically consist of a powder formulation and a device. The formulation, which contains active pharmaceutical ingredient(s) (APIs) micronized to inhalable particle size and a few excipients may, at first glance, appear simple. However, a large number of factors are critical to the performance of dry powder formulations for inhalation. Furthermore, many of these interact in complex ways. The articles in this two-part series will focus on adhesive mixtures for inhalation, also called ordered mixtures or carrier-based formulations. These terms stem from the formulation structure of carrier particles with fine drug particles attached to their surfaces. In the first article, we will discuss considerations relating to the four parts that together define a dry powder formulation. In the second article, important modes of interaction will be analyzed, along with the interplay between the device and the formulation. Our vision is that in-depth knowledge of the four parts that define a formulation and the ways they interact can lead to improved formulation development in the future.

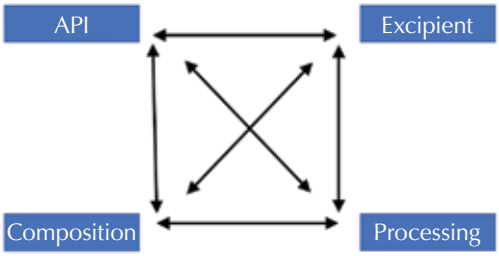
Four parts define the dry powder formulation

A dry powder inhalation (DPI) product, consisting of the device and the formulation, has four key parts which together define the formulation: the active pharmaceutical ingredient (API), excipient(s), composition and processing. As illustrated in Figure 1, all of these interact with each other. Dry powder formulation development is therefore a complex and challenging task, typically involving a range of experimental design campaigns.

The simplest type of adhesive mixture consists only of fine active pharmaceutical ingredient (API) particles and (pharmaceutically inert) carrier particles, as schematically illustrated in Figure 2. Fine excipient particles and coating agents may be added to this mixture [1, 2]. Lactose monohydrate is, by far, the most common excipient and we will assume the use of lactose throughout this article, both for carrier and fine particle excipients, unless otherwise stated. As for coating agents, magnesium stearate (MgSt) is the most popular and now present in several products on the market [3]. Regardless of the simplicity or complexity of the formulation, the API, excipient(s), composition and processing together determine the dispersibility of the powder, expressed by the fine

Figure 1

The four parts that together define an inhaled formulation and their interactions.



particle fraction (FPF). Besides dispersibility, the stability of the inhaled product (both chemical and physical stability) is critical and must be monitored continuously during development work. That discussion is, however, outside the scope of this article.

Key pharmaceutical requirements

Apart from standard pharmaceutical requirements for assay, degradation products, appearance, homogeneity and uniformity of dose, a key requirement for inhalation products is that the formulation is dispersed in the inhaled air stream in an efficient, robust and reliable way. The fine particle dose (FPD), normally defined as the amount of drug in the aerosol cloud in particles with an aerodynamic particle size less than 5.0 µm, is a key measure, as this is the API dose that can reach the lungs. The fine particle fraction (FPF) is defined as the fine particle dose divided by the delivered dose and is therefore a quality measure, as it directly relates to the efficacy of the inhaled product. The challenge for a developer is that FPF is not easy to understand nor to control, as it is affected by a range of formulation factors as well as other considerations. This also means that if changes in FPF occur during scale-up or running production, it can be challenging to make adjustments and reestablish the product performance.

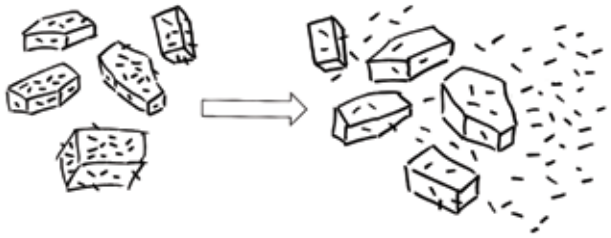
The active pharmaceutical ingredient (API)

In most cases, the fine API particles are produced by the micronization process of jet milling [2]. This process is well suited for production of particles in the size range of 1-5 µm, the optimal size range for inhaled delivery.

The API particles should preferably be crystalline with a narrow particle size distribution. But as micronization can be a very harsh process, the micronized API often contains considerable amounts of amorphous material. This may pose a risk to the drug product, impacting both chemical degradation and physical changes. Ideally, therefore, full crystallinity of the API should be restored in a so-called "conditioning" process, e.g., by exposing the micronized drug to controlled relative humidity (RH) [4], or alternatively to ethanol vapor. By thorough method development and tight control of RH or ethanol activity (RE), particle growth during the conditioning process can be kept to a minimum.

Figure 2

Schematic illustration of an adhesive mixture consisting of carrier particles with attached fine API particles (left). During inhalation, the fine drug particles must detach from the carrier particles and disperse in the inhaled air stream (right) to be able to reach to the lungs.



Spray-drying of API-containing solutions or suspensions is another route to the production of inhalable particles [2, 5]. Spray-drying for inhalation is becoming increasingly popular and is often the preferred route for biomolecular drugs. However, we will not discuss spray-dried particles in detail here because they may not be the first choice for formulating adhesive mixtures.

The micronized API consists of fractured irregular particles that, in most cases, are extremely cohesive, which is why formulation approaches are needed. Particle size distribution is the most critical API property, as it directly relates to the fraction of API that is able to reach to the lungs, but other important API parameters have also been investigated [6]. For example, the shape and surfaces of micronized particles may vary considerably among APIs and such differences will strongly influence dispersion behavior. Despite extensive research, including work in the fields of solid state and material sciences, it is still not possible to predict the dispersibility of a micronized API. Attempts include methods based on atomic force microscopy (AFM) to measure the force between the API and (carrier) lactose [7, 8]. AFM can also be used for assessment of the cohesive-adhesive balance (CAB) [9]. Several other properties of the micronized API contribute to dispersibility, for example, frictional properties [10]. Additional API properties that should merit attention include mechanical properties, which will be discussed in the processing section of this article.

A way to circumvent the challenge of assessing the cohesiveness and dispersibility of the API is to perform pre-formulation studies using relevant excipients, compositions and mixing conditions. Analysis of FPF data may then enable calculation of the "apparent dispersibility" of the API in the relevant type of formulation [11, 12].

The excipients

Lactose carrier

The main excipient, by weight, in the adhesive mixture will always be the carrier. Within the carrier size range of approximately 50-300 µm, there are multiple grades of lactose for inhalation from which to select. The choice of carrier has a major impact on formulation performance and a range of carrier

properties have been identified as critical. Of these, size, shape, surface properties and content of fine particles (i.e., "carrier fines") are considered to be the most important [6, 13].

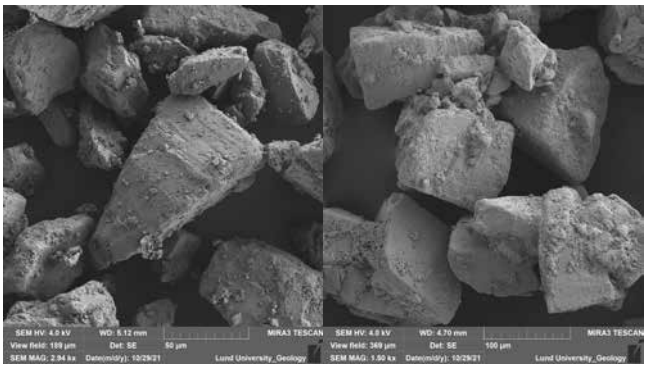
The effect of carrier particle size has been much investigated but the experimental findings are often puzzling. To date, no general theory has been established for the way in which carrier particle size affects the FPF. It is clear, however, that a larger carrier contributes to improved flowability of the formulation, which is particularly important for reservoir DPIs. On the other hand, a larger carrier size means a lower specific surface area, which limits the drug loading capacity.

Two principal types of carriers can be identified and both have their merits. In addition, some lactose grades will exhibit properties of each:

- Single crystal carriers with the typical "tomahawk" shape
- Aggregated crystal carriers

Figure 3

Examples of lactose carrier particles: tomahawk type (left) and aggregated carrier type (right). Note the difference in image magnification: left image = 2.94 kx, right image = 1.50 kx. Courtesy of Anders Widelöv, Magle Chemoswed AB, Sweden.



In both types, the surfaces are irregular at the nano-scale and micro-scale due to manufacturing process and there are micropores and indentations on the surfaces, (Figure 3). In addition, aggregated carriers have larger and wider cavities and clefts, which are able to carry considerable amounts, i.e., "chunks" of the micronized API. These cavities provide shelter for the API particles during mixing as well as during dispersion, which is why aggregated carries behave quite differently from single crystal carriers [14]. Additional challenges with lactose as an excipient include surfaces that may be contaminated by protein residues or other unwanted material [15] and that may contain amorphous regions. Such regions may negatively affect both the dispersibility and the stability of the formulation and should therefore be kept to a minimum.

Lactose fines

Lactose fines (or fine particles of another pharmaceutically inert material) can be added to the adhesive mixture. The median particle size of such grades is typically less than 10 µm. The main effect of lactose fines is to improve the dispersibility of the formulation and various hypotheses have been put forward to explain the effect [16]. From a "formulation mechanics" perspective, the effect of these inert fine particles is the same as that of the API [11, 17, 18]. Therefore, added lactose fines can reduce flowability of the formulation, (which will be discussed in the second part of this article).

Some carrier grades already on the market—in particular, the milled grades—contain fine lactose particles. Use of these may speed up formulation development as the performance of the binary API/carrier mixture may be acceptable without further additives. However, grades with a fixed content remove the opportunity to use fine lactose content as a tool to adjust performance.

Figure 4

Lactose carrier particles (Respitose SV003) coated with 1.0% magnesium stearate at 5, 15 and 25 minutes of coating time in a high shear mixer. The red color indicates magnesium stearate and the green color indicates lactose. (See reference 20.) Reproduced with permission from Elsevier.

Coating agents

Excipients that are smeared onto the other constituents of the formulation are called "coating agents" in this article. Alternative names in the literature are "lubricants" and "force control agents." Currently, the most common coating agent, used in a number of DPIs, is magnesium stearate (MgSt) [3]. Other materials that can have a similar effect are L-leucine and sodium stearyl fumarate [19], but these have not yet found their way to the market. When preparing an adhesive mixture containing a coating agent, it is common to combine the carrier with the coating agent in a first process step (the coating step) and thereafter add the API(s) and optional fines, but other process schemes may be considered [2]. A recent study demonstrated visualization of the coated layer and quantification of the degree of surface coverage for three different coating agents using time-of-flight secondary ion mass spectrometry (TOF-SIMS) [20]. For illustration, the coating of lactose carrier with magnesium stearate is shown in Figure 4.

Application of a coating agent is known to significantly enhance the dispersibility of DPI formulations with respect to FPF. The mechanism is not fully understood but is believed to be a combination of lowered surface energy and reduced friction among particles [10, 21]. Both the amount of coating agent and the coating process have been shown to be critical, as is described in the processing section of this article. In addition, application of coating agents may have implications for formulation stability. On the negative side, chemical incompatibility between MgSt and some drugs, e.g., acetylsalicylic acid, has been reported [22]. However, if there is chemical compatibility, physical stability may be improved by the addition of a coating agent, as the moisture sensitivity of the dry powder formulation could be reduced, for instance, by addition of hydrophobic MgSt.

Composition

The composition of the adhesive mixture, i.e., the relative proportions of API(s) and excipients, is a key factor influencing formulation properties and performance. The maximum drug load of an adhesive mixture has been a topic of debate [2]. Increasing the drug load of the formulation will, sooner or later, lead to a segregated system, as the carrier surfaces become overloaded with drug. A conservative view states a limit of approximately 5% drug load w/w, but this may be increased, for instance, with aggregated carriers where the cavities and clefts can accommodate larger amounts of the API [2]. Given the dose, in terms of the amount of powder to be inhaled, also is limited to approximately 50 mg per inhalation, this sets an upper limit for how large a dose can be administered by adhesive mixture technology to approximately 2.5 mg of API. For drugs such as antibiotics, where much higher inhaled doses are required, adhesive blends are therefore not an option [2].

The use of the terms "adhesive" mixture and "ordered" mixture stems from the picture of carrier particles covered with a layer of the fine drug particles on the surfaces. The drug load corresponding to a monolayer of API particles on the carrier surfaces (a surface coverage ratio (SCR) of 1), can be calculated based on the (enveloped) surface area of the carrier and the API [17, 23]. The SCR and the associated "blend state" are therefore key features of the formulation. In reality, however, such well-ordered structures are usually not found. Instead, many APIs tend to form small clusters adhering to the carrier surfaces, and with increasing API load, a multi-layer structure is often formed [17, 18].

Many inhalation drugs, including corticosteroids, β-agonists and muscarinic agonists, are highly potent, with doses ranging from single digit µg to a few hundred µg. For such low doses, the formulation challenge is achieving a homogeneous and high performing formulation when the drug content is less than one percent. Due to the small particle size, the number of API particles in a dose is still enormously large and homogeneity is usually not an issue, at least down to approximately 0.1% drug load (see the processing section of this article). However, formulations with a low drug load tend to yield a very low FPF, which means that a large fraction of the drug is not able to reach to the lungs and therefore will not contribute to the pharmacological effect. The low dispersibility is often attributed to the irregular surfaces of the marketed carrier grades. Forces acting between particles during mixing, called "press on forces," have been suggested as another explanation [24], although a strict definition of such forces has not been given.

Addition of lactose fines to increase the "total fines" concentration, i.e., the sum of fine particles from API(s) and excipients in the formulation, is a way to improve the FPF [16]. Data on the effect of added

lactose fines are given in Figure 5 and compared to the effect of an increase in drug load. In both cases, there is an almost linear increase in the FPF within the investigated interval. However, at even higher concentration, the FPF starts to fade [11].

As for the addition of MgSt or other coating agents, small amounts are normally sufficient and the typical range used is from 0.1% to 1.0%. [2, 3]. It should be noted, however, that complete coverage of the carrier particles with a coherent layer of coating agent cannot be expected when the coating agent is applied in a dry coating process. This is illustrated in Figure 4, where small areas of uncoated lactose (green) appear, regardless of the mixing time.

Processing

The two main routes for mixing are low shear mixing and high shear mixing [25]. Low shear mixing is carried out in tumbling mixers, such as the Turbula® (Willy A. Bachofen, Basel, Switzerland) or Bohle (LB Bohle, Ennigerloh, Germany) mixers, with speeds from tens of revolutions per minute (rpm) (or even lower at production scale) to one hundred rpm and mixing times typically ranging from 15 minutes to 1 hour. Tumbling mixers are usually gentle and can operate without causing substantial damage to crystalline materials. Low shear mixing is appropriate for binary API/carrier blends and for ternary blends that include lactose fines. Attention should be paid to mixing of highly cohesive APIs, as the applied forces may not be sufficient to break up API agglomerates.

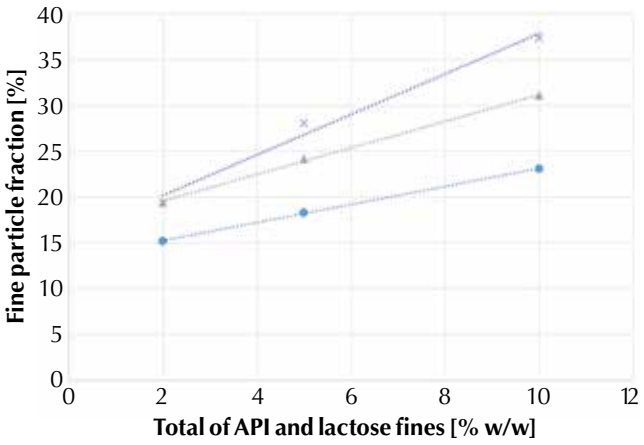
High shear mixers are more efficient than low shear mixers and a few minutes of mixing is normally sufficient to achieve good homogeneity. High shear mixing is also recommended for compositions with coating agents, as these agents are more easily smeared with high shear mixing [26]. Still, coating may occur in a tumbling mixer [27]. A comparison of three different coating agents revealed that MgSt coated a lactose carrier more rapidly than did sodium stearyl fumarate and L-leucine using a Diosna high shear mixer (Diosna Dierks & Sohne, Osnabrück, Germany) [20].

A main drawback of high shear mixing is that it may lead to generation of amorphous content during processing which, in turn, could induce stability issues. The effect is expected to be more pronounced for larger carriers and at higher speeds. Addition of a coating agent may reduce such effects, as the surfaces become coated as well as lubricated, which protects the underlying lactose crystal lattice. Losses of drug and powder will likely also be larger in high shear mixers than in low shear mixers.

Mixers that are even more intense, such as the Cyclomix (Hosokawa Micron, Runcorn, UK) and the Nobilta™ (Hosokawa Micron, Runcorn, UK), have also been investigated for preparation of inhaled formulations. These mixers act through a combination of high shear and forces applied directly to the (confined) particles, in what is sometimes referred to as a "mechanofusion" process [26, 28]. When used for coating of lactose carriers, obtaining a powder with exceptionally good flow properties has been reported [28, 29]. It can be questioned, however, whether such high-energetic, expensive processes are needed for preparation of adhesive mixtures for inhalation.

Figure 5

Fine particle fraction plotted as a function of the total content of API plus lactose fines. Circles refer to budesonide and carrier A, triangles to budesonide and carrier B, and X's to 2% budesonide and carrier A, with increasing amounts of lactose fines. Adapted from reference 11.



Advances have been made in understanding the forces exerted among particles during high shear mixing and how these affect formulation performance in terms of FPF [19].

The key concept here is the applied mixing energy (ME), which is defined by:

$$ME = m_{carrier} * v^3 t / r \qquad \text{Equation 1.}$$

where $m_{carrier}$ is the mass of the carrier particle, v is the peripheral speed, r is the radius of the mixing bowl and t is the mixing time. With revolutions per minute (rpm) instead of peripheral speed, the equation reads:

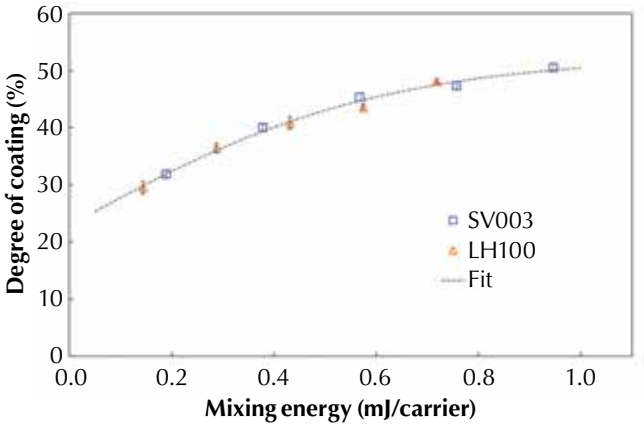
$$ME = 8\pi^3 m_{carrier} * \left(\frac{rpm}{60}\right)^3 r^2 t \qquad \text{Equation 2.}$$

Analogously, the applied mixing force (MF) can be defined by:

$$MF = m_{carrier} * \frac{v^2}{r} \qquad \text{Equation 3.}$$

Figure 6

The degree of surface coating plotted versus the applied mixing energy (ME) for coating of lactose carriers SV003 (squares) and LH100 (triangles), both from DFE Pharma, Goch, Germany, with 1.0% L-leucine. The fit is made based on the combined dataset. Error bars indicate ± 1 standard deviation. (Data from reference 19.)



It should be emphasized that the mass of the carrier is key both to mixing energy and mixing force. As carrier mass is proportional to the cube of the particle diameter, this shows the major impact of carrier particle size in high shear mixing.

In a recent study [19], the mixing energy concept was utilized for smearing of coating agent onto lactose carrier. Two single crystal carrier grades, Lactohale LH100 (DFE Pharma, Goch, Germany) and Respitose SV003 (DFE Pharma, Goch, Germany), were coated using 1.0 % L-leucine. Respitose SV003, which is the smaller carrier, was coated at a higher speed and for longer processing times. When plotted as function of the applied ME, however, the two curves become perfectly superimposed, (Figure 6). This illustrates the validity of the ME concept and shows that for a smaller (i.e., lighter) carrier, a higher speed and/or a longer coating time is needed to achieve the same degree of coating.

Looking to Part 2 of this series

In this Part 1 article, we have considered four key parts that define a dry powder formulation: the active pharmaceutical ingredient (API), excipients, composition and processing. In the second article, we will show that the mixing process may strongly affect the dispersibility of the formulation and that the applied mixing energy can be used to understand and predict the fine particle fraction. In addition, the interplay between the formulation and the device will be discussed.

Acknowledgement

This work was supported by the Swedish Foundation for Strategic Research.

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