Formulation development of adhesive mixtures for inhalation—A multi-factorial optimization challenge: Part 2

Addressing complex interactions among the four parts of a dry powder formulation

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Synopsis

In the first of two articles in this series, we described the four parts that, together, constitute a dry powder inhaler (DPI) formulation, i.e., the active pharmaceutical ingredient (API), the excipients, the composition and the blending process. Each of these must be thoroughly understood in order to develop and optimize adhesive mixtures for inhalation. In this second article, we give examples of interactions among the different parts. Moreover, the influence of the device is discussed. Obviously, the formulation and the device must work well together as their combined action determines the pharmaceutical performance of the inhaled DPI product.

Complex interactions

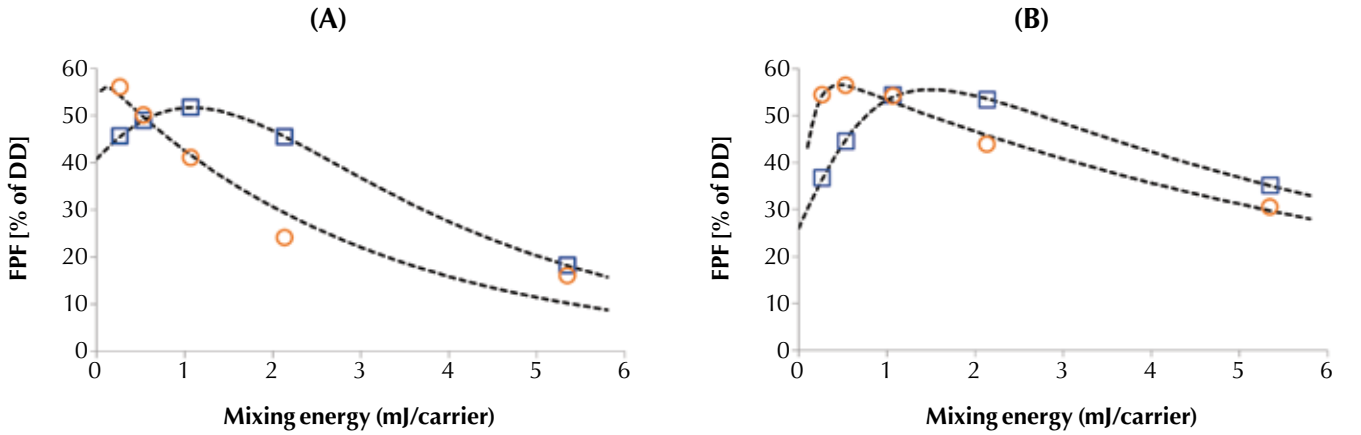
The active pharmaceutical ingredient (API) (or APIs in a combination drug product), the excipients, the composition and the processing are all critical to the performance of a dry powder inhaler formulation [1]. Furthermore, these four parts interact in complex ways. The challenge for the formulation scientist is to capture the nature of the interactions and design experiments that enable quantification of the interaction effects. In principle, development work would be carried out by varying all relevant parameters within reasonable limits in an extensive design of experiment (DOE). However, besides being extremely costly in labor and materials, a complication with this approach is that many interaction effects are multi-factorial and non-linear, which makes them difficult to unravel in such designs. We will present examples of complex interactions and discuss how they can be understood.

The interaction between processing and composition for formulations with a coating agent

A complex interaction is one among the drug, the coating agent (also called the force control agent), the composition and the mixing process. An extensive study on formulations that include coating agents blended using high shear mixing was recently published [2]. The performance of budesonide (Bud) adhesive mixtures with leucine-coated lactose carrier, shown in Figure 1, can serve as an example. Dispersibility profiles for 1% and 5% Bud in adhesive mixtures with 1% leucine are plotted as function of the

Figure 1

Fine particle fraction as a percentage of delivered dose for formulations consisting of Bud and lactose carrier Lactohale LH100 (DFE Pharma, Goch, Germany), with leucine as a coating agent, administered using the "Screenhaler" prototype dry powder inhaler. The leucine concentration is 1% in A and 3% in B. Circles refer to 1% Bud and squares to 5% Bud. Adapted from reference 2.



applied mixing energy in Figure 1A, and corresponding profiles for formulations with 3% leucine are shown in Figure 1B. The equation for calculating the mixing energy, ME, was presented in the first article and can be written as:

$$ME = 8\pi^3 m_{carrier}\left(\frac{rpm}{60}\right)^3 r^2 t \qquad \text{Equation 1.}$$

where $m_{carrier}$ is the mass of the carrier, t is the mixing time, r is the radius of the mixing bowl and rpm is the speed in revolutions per minute.

Along the same lines, the mixing force exerted, MF, can be expressed by:

$$MF = 4\pi^2 m_{carrier}\left(\frac{rpm}{60}\right)^2 r \qquad \text{Equation 2.}$$

The dotted lines in Figures 1A and 1B are generated using modeling equations that address both the fine particle fraction (FPF) increase and subsequent decrease, using rate constants k1 and k2, respectively.

$$FPF = \left[A + \frac{B}{1+e^{-k_1 x}}\right]\left(e^{-k_2 x}\right) \qquad \text{Equation 3.}$$

where x is the mixing energy, per Equation 1. As is seen in Figure 1, the dotted lines fit well to the data, which means that the rate constants k1 and k2 describing the increase in FPF and the subsequent decrease in FPF can be calculated. These rate constants are specific to the interaction between the API and the coating agent but also depend on the composition. Rate constants for the studied Bud/leucine systems are shown in Table 1. As can be seen, the initial increase in FPF occurs more rapidly for 1% Bud formulations than for 5% Bud formulations.

Table 1

Rate constants k1 and k2 for Bud/leucine formulations, obtained using Equation 3.

System		k1	k2
1% Leucine	1% Bud	>20*	0.33
	5% Bud	1.2	0.31
3% Leucine	1% Bud	9.4	0.13
	5% Bud	1.9	0.14

*could not be precisely detected

This can be explained by assuming that the mechanism behind the FPF increase is related to smearing of coating agent onto the API, which will take longer for a higher drug content. As for the subsequent decrease in FPF, the rate constant seems to depend on leucine concentration only. It is pointed out that the FPF level obtained also depends on the inhaler used, as will be discussed below.

Investigations indicate this type of behavior is common. For instance, the same type of curve was observed for three different coating agents (magnesium stearate, leucine and PRUV), for two different drugs and for formulations with and without added lactose fines, further analyzed using different inhalers [2].

The interaction between the mixing process and the composition for formulations with a coating agent, therefore, provides general insight, which helps shed light on some of the much-debated questions regarding performance of adhesive mixtures. It can be concluded that:

- Carriers of different size (mass) should not be compared using the same mixer speed, as this will provide different force fields in the mixing process.

- There is a range of optimal mixing. Both too little mixing and too much mixing should be avoided.
- FPF is not always higher for a higher drug load—it depends on the applied mixing energy. In Figure 1, it can be observed that 1% Bud formulations achieve similar or even higher FPF values than 5% Bud formulations when mixed using low mixing energies.
- The size of the mixing bowl is critical, as the mixing force relates to the bowl radius. Therefore, the mixing energy equation gives information about how to adjust speed during scale-up.
- A higher concentration of coating agent is not necessarily better. The difference in maximum FPF level between Figures 1A and 1B is marginal.

Our view is that the optimal mixing point should be attained shortly after reaching the maximum in FPF. An advantage of being on the (weak) slope is that it is possible to adjust FPF merely by adjusting mixing time or speed. This means that the formulator possesses a quality by design tool that makes it possible to fine-tune fine particle dose independently of delivered dose, thereby maintaining both key attributes within specification.

Processing effects for formulations without a coating agent

Formulations without a coating agent may also show important interactions between the composition and the mixing process. However, the initial increase in FPF

is not seen in these systems. This is illustrated in Figure 2, where fine particle fractions of a 2% Bud binary formulation are compared to the 1% Bud/1% leucine formulations at different mixing energies.

Further insight can be obtained from analysis of data published by researchers from the University of Kiel, who investigated high shear mixing of 1.5% Bud/lactose carrier blends, further containing 7.5% added lactose fines [3, 4]. A two-step mixing process was applied and two protocols were evaluated: one in which Bud was added first and one in which the lactose fines were added first. For each mixing procedure, a range of batches were manufactured by vary-

Figure 2

Comparison of fine particle fractions between coated and uncoated batches. Squares refer to a composition with 1% Bud/1% leucine, triangles to a 2% Bud formulation without a coating agent. Lactohale LH100 was used as a carrier in both cases and no lactose fines were added. Data was derived from reference 2.

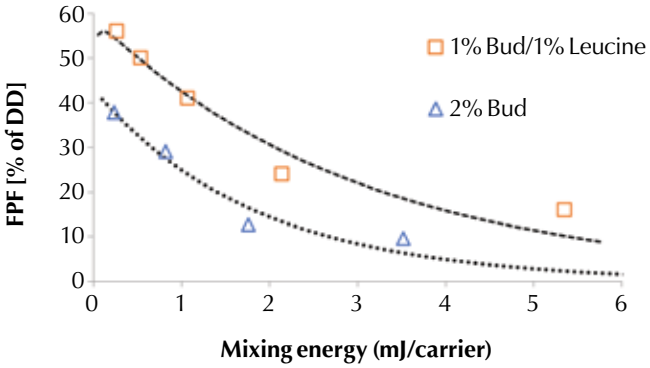
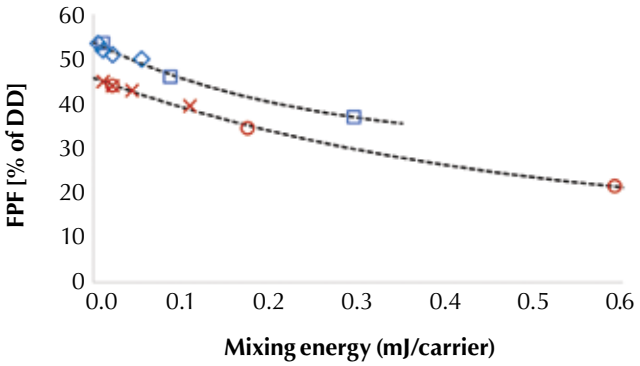
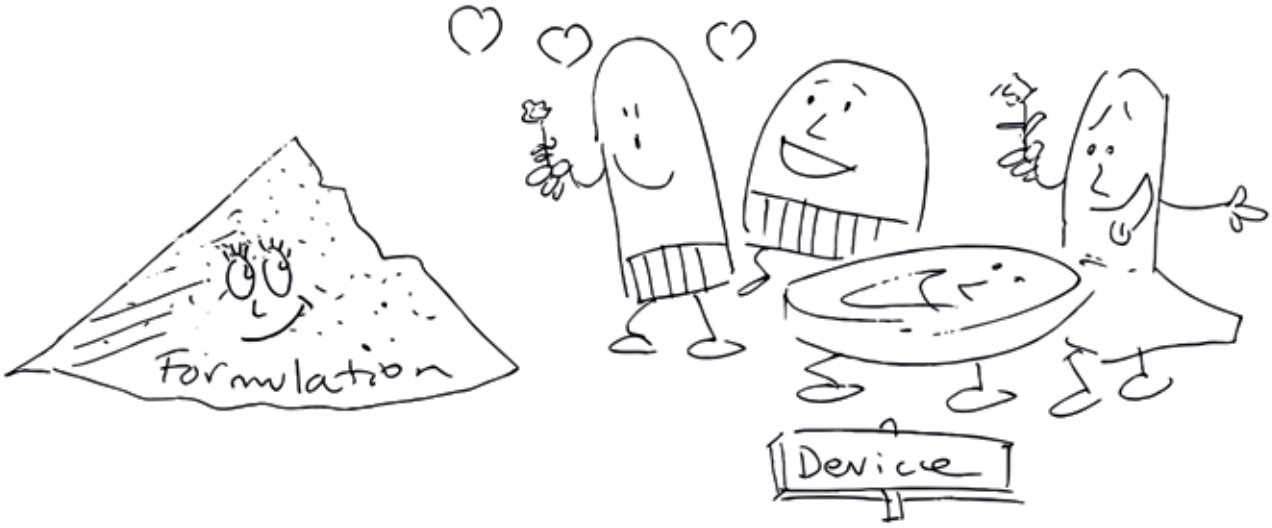


Figure 3

Fine particle fraction of Bud plotted versus the applied mixing energy for a two-stage high shear mixing process. Circles and X's refer to batches where Bud was added first; circles show mixing speed was varied; X's show mixing time was varied. Squares and diamonds refer to batches where lactose fines were added first and Bud was added in the second step. In this case, only the mixing energy of the second step is relevant to Bud. Squares show varying mixing speed; diamonds show varying mixing time. Dashed lines refer to exponential decay modeling equations. Data were extracted from reference 3.





ing mixing time or speed and were analyzed using the Novolizer® dry powder inhaler (Meda AB, Solna, Sweden). Figure 3 shows FPF data from this study, plotted as function of the mixing energy per Equation 1. It can be observed that for both mixing procedures, an exponential decay in FPF as a function of ME results. Batches mixed at different times fall on the same curve as batches mixed using different speeds, which further supports the validity of the mixing energy concept. The FPF decrease can be described by an exponential decay function (Equation 4):

$$FPF = Ce^{-kx} \qquad \text{Equation 4.}$$

where x is the applied mixing energy. This is the same type of exponential decrease as that observed with extended mixing for systems including a coating agent, which points toward similar mechanisms for the two cases.

For low shear mixers, there are relatively few studies of the influence of the mixing process [5, 6]. In general, a slight decrease in FPF is seen as function of mixing time. Overall, processing effects are believed to be less marked in low shear mixing. Instead, the formulation challenge resides in achieving a powder blend with good drug content uniformity [5].

Formulation interactions with the device

To get the full picture, the device obviously must be considered. Conceptually, the device interacts with the entire formulation and the resulting performance, in terms of FPF, is governed by the balance between the (attractive) forces among the particles in the formulation and the dispersion forces generated via the inhaled air stream. Both the type and magnitude of the dispersion forces matter. An overview of different dispersion mechanisms is provided in reference 1. For adhesive mixtures consisting of adhesive units of carrier and fine particles, the main types of dispersion forces are:

- Inertial forces due to:
  - Wall collisions (adhesive units colliding with the walls inside the inhaler)
  - Particle/particle collisions (collisions between adhesive units)
- Drag and lift forces (when the velocity of the surrounding air is much higher than the velocity of the adhesive unit)
- Shear and frictional forces

The geometry of the flow path through the device and the inspiratory flow profile determine the types and magnitudes of the dispersion forces. Formulation design can, however, also affect which dispersion forces come into play. For instance, drag forces may not contribute to the dispersion of API particles residing in cavities and clefts, i.e., of an aggregated carrier, as these cannot be accessed by the airstream. Moreover, the size of the carrier particles will affect the magnitude of the impact forces, as larger carriers will accelerate slower and, therefore, impact at lower velocities. However, a detailed analysis of the types and magnitudes of dispersion forces is outside of the scope of this article.

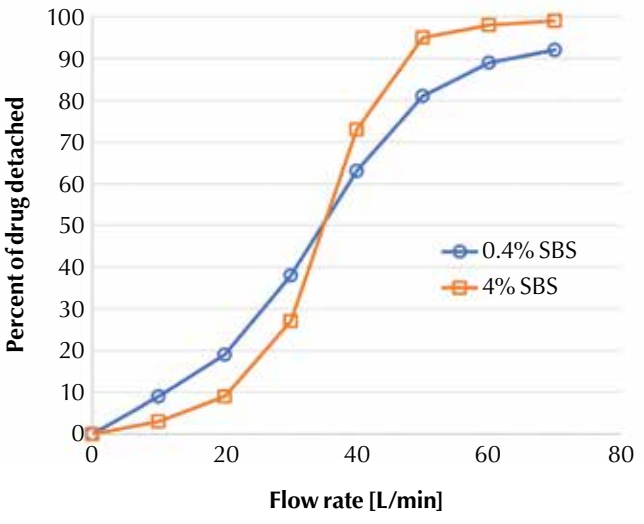
Requirements for formulation flowability

Formulation flowability must be assessed to ensure a good match between the formulated powder and the device. The demand on powder flowability depends on whether a device-metered (reservoir type) inhaler or a device using pre-filled doses in capsules or blisters is to be used. For device-metered inhalers, good flowability is a prerequisite for fulfilment of regulatory demands on delivered dose and delivered dose uniformity, as the powder needs to flow from the reservoir into the dosing cavity during metering of the dose. In the case of pre-metered doses, powder flowability must still be adequate to allow for industrial-scale high-speed filling. The relationship between powder properties and filling performance has been investigated for capsule fillers and drum fillers, respectively, in references 7 and 8.

Once the inhaler is filled, sufficient powder flowability is needed for entrainment of the dose from the dose-holding compartment (such as a cavity or capsule). Incomplete entrainment obviously would lead to compromised doses and issues with delivered dose uniformity. For capsule devices, there may be a risk of incomplete emptying from the capsules when using large carrier particles since piercing of the capsules, performed *in use* by the patient, will not always be ideal.

Figure 4

The percentage of salbutamol sulfate, SBS, detached from the carrier in a cyclone inhaler prototype, for systems of 0.4% SBS plus carrier (circles) and 4.0% SBS plus carrier (squares) as function of air flow rate. At flow rates below 35 L/min, the 0.4% formulation shows better dispersibility, while at flow rates higher than 35 L/min the 4.0% formulation gives higher FPF values. It should be noted that the percent of drug detached from the carrier is not the same as the FPF, but it can be anticipated that the two measures correlate.



In part 1 of this two-part series, we saw that both increased drug load and addition of fine lactose can improve the dispersibility of a formulation [9]. At the same time, however, both of these measures can entail a reduction in powder flow, with associated risks for issues in filling and dosing as mentioned above. The challenge for the formulator is to find the optimal balance between the two approaches. Again, this emphasizes the need for careful selection of a device and filling method, and assessment of a good match between a device and the formulation.

Prediction of optimal dispersibility

Models have been put forward for selection of excipients (carriers and fines) as well as composition, in order to maximize formulation performance. Shalash, et al., developed a model in which dispersibility can be predicted from measurement of the nano- and micro-porosity of the carrier in combination with the fluidization energy of the formulation [10, 11]. The model was tested using 1% fluticasone propionate formulations with a range of different carrier materials and good correlation was obtained (however, a mannitol carrier was an outlier) [11, 12]. Hertel, et al., used permeability data from a powder rheometer to investigate optimum composition with respect to addition of lactose fines [13].

While basically sound, the generality of these models remains to be proven, e.g., for inhalers with different dispersion principles. Moreover, formulations with a coating agent may not be applicable, as the surface properties of the carriers will be extensively changed after processing. To circumvent the uncertainties associated with these models, it is recommended that studies be performed early in project development, in the relevant mixer, to map out dispersibility as well as delivered dose uniformity for the selected device. Furthermore, if a high shear mixer is to be used, such mapping should include the effect of the applied mixing energy.

Flow rate and formulation performance

A primary parameter of an inhalation device is its air flow resistance, as this determines the flow rate at which DPI performance should be assessed. A pressure drop of 4 kPa over the device is recommended by the European Pharmacopoeia for testing [14]. Still, patients will use DPI products over a wide range of pressure drops/flow rates. The flow rate behavior is, therefore, important and has been investigated by several groups, as reviewed by Elsayed and Shalash [12]. Both monotonic and sigmoidal curves have been reported for FPF as a function of flow rate, and in some cases, even bi-exponential curves have been observed [15].

To date, a general understanding of flow rate dependence has not been obtained, which, in part, may be due to the extensive differences in design and, therefore, different modes of dispersion of various DPI

devices. In this context, it is relevant to bring up the interplay between the formulation and the flow rate reported by researchers at the University of Groningen [16, 17]. For the systems studied, sigmoidal flow rate dependencies were obtained when analyzed in a prototype inhaler equipped with a cyclone mouthpiece. As illustrated in Figure 4, a crossover in FPF performance can occur as function of flow rate, i.e., at a low flow rate, the formulation with low drug load gives the highest FPF, while at high flow rates, the situation is reversed. This phenomenon can be understood by realizing that above a certain drug load, the API particles start to form a connected layer at the carrier surfaces that requires additional energy to break up. Such networks of connected API particles were also demonstrated by the Groningen authors [17].

Therefore, to avoid flow rate sensitive formulations, it is recommended that FPF studies be performed at different flow rates/pressure drops early in the development process. If a sigmoidal dispersibility profile is found, it should be ascertained that flow rates/pressure drops achieved by patients fall above the zone with the steep FPF increase. As further demonstrated by the Groningen authors, similar effects can occur due to the presence of lactose fines. When 4% fine lactose (named FLF in their paper) was added to a 0.4% Bud formulation, the FPF versus flow rate curve changed from monotonic to sigmoidal [18]. Again, this points towards the total amount of fine particles, i.e., API(s) plus fine lactose, as a critical parameter for formulation performance.

A final challenge for multi-dose devices is to avoid retention and build-up of the API within the device. This may prove challenging for devices that have strong deaggregation capability due to inertial impaction on device surfaces, which tend to have more powder build-up and, therefore, higher levels of drug retention in the device. Cleaning of the mouthpiece may therefore be required, unless a disposable device is used.

Summary

This article focuses on the pharmaceutical performance of adhesive mixtures for inhalation, also called ordered mixtures or carrier-based formulations. Adhesive mixtures consist of four parts: the API(s), the excipient(s), the composition and the processing. Several features from each part are critical to performance. Moreover, there are interactions among all four parts, many of which are highly complex. The challenge for the formulator is to understand the nature of the interactions and design experiments to correctly capture and quantify the effects.

Binary formulations of API and lactose carrier can, in many cases, be blended using a low shear blender, which can offer the advantage of not damaging particles, provided the applied mixing force, MF, is not too strong. The main challenge will be to achieve good blend uniformity, while dispersibility is less affected by the mixing process. Addition of fine lactose particles is a means to improve formulation performance with respect to FPF.

Formulations that include a coating agent display complex behavior. To ensure efficient smearing of the coating agent, the use of a high shear blender is recommended. The processing parameters will be critical to performance and must be thoroughly investigated. The applied mixing energy, ME, which combines the effects of carrier mass, bowl size (radius), mixing time and speed, has been identified as a key parameter that governs performance in terms of FPF. This parameter, together with the mixing force, MF, is believed to be key to understanding how particles are affected in the mixing process, and can be expected to facilitate formulation development as well as scale up.

The interaction between the formulation and the device is another complex relationship. The air flow resistance of the device determines the flow rate to be used for performance characterization of the DPI product and the flow path geometry determines the modes available for fine particle dispersion. The device, therefore, plays a vital role with respect to the dispersibility of the inhaled drug product and may also set other requirements, for instance, regarding powder flowability.

Furthermore, the device is obviously the interface to the user. The patient sees and interacts with the device but hardly experiences the formulation, except for a faint taste upon inhalation. Therefore, the device/patient interface is the driver for a positive patient experience and user (handling) studies in patient populations are a part of the DPI product development process and registration.

Acknowledgement

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