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Developing an Orally Inhaled Dry Powder Formulation—A Complex Itinerary and a Technological Challenge

A Q&A with Gonçalo Andrade, business development manager at Hovione

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mona plougmann/E+/Getty ImagesThe delivery of an orally inhaled API to the deep lung can be performed using different drug-delivery platforms, such as nebulizers, pressurized metered dose inhalers (pMDI), and dry powder inhalers (DPI). DPIs are increasingly becoming a more important drug delivery option and are expected to hit double-digit figures, reaching global sales of $31.5 billion in 2018 (1).

DPIs are conventionally formulated using a carrier-based approach, in which the API is size-reduced until it reaches an inhalable particle size and is further blended with a lactose carrier to enable dose metering and to improve powder flowability and dispersibility. Even though this formulation approach is the most commonly used, it presents several drawbacks. To overcome the limitations, as well as to address the renewed interest in pulmonary delivery of biotherapeutics and other advanced therapies, several alternative particle engineering approaches have been devised over the years, such as the production of composite particles by spray-drying where the API is embedded in an excipient matrix.

Although the development of a DPI seems straightforward, it is a complex area that integrates multiple fields of knowledge. In a general way, the success of a DPI produced using a carrier-based formulation approach will be determined by the API physicochemical properties, the formulation composition and process, the device and operating conditions, the patient–device relationship, the environmental variables, and ultimately, patient compliance. In this article, Gonçalo Andrade, business development manager at Hovione, spoke to *Pharmaceutical Technology* about the key considerations when developing an orally inhaled dry-powder inhalation formulation.

PharmTech: What causes agglomeration of drug particles in DPI formulations and how does it affect drug delivery into the lungs?

Andrade: Regarding the carrier-based approach, it is generally recognized that the API particles should have an aerodynamic particle size between 1 to 5 micron for optimal deep-lung targeting. However, such small particles are characterized by a high surface energy; therefore, they tend to be very cohesive and prone to agglomeration, which can not only lead to uniformity challenges upon formulation with other excipients but also result in poor flowability and dispersibility of the drug dose during aerosolization.

The agglomeration behavior of the drug particles is primarily dictated by the API processing history. Primary (e.g., crystallization) and secondary (e.g., top-down technologies such as jet milling) processing confer specific attributes to the API particles, which will ultimately determine the cohesion (API–API) and adhesion (API–carrier) forces of the API. It is, therefore, clear that the particle engineering technologies used to size-reduce the API crystals will impact the powder interfacial properties and consequently, the powder fluidization and aerosolization.

Although there are several particle engineering technologies available, jet milling (JET) is still the most commonly used. In this case, the particle comminution is based on particle–particle and particle–wall collisions due to the turbulent stream created by the insertion of a grinding gas. On the other side, through a wet polishing (WET) approach, the API is suspended in an anti-solvent system and is size-reduced by particle–particle and particle–wall collisions, being then isolated by spray drying to obtain a dry powder as the final product. The presence of an anti-solvent during the WET comminution process reduces the high energy input that occurs at the particle surface during the JET micronization process, preventing the creation of local hot spots that could result in the formation of undesirable product properties such as amorphous domains and/or changes in the API polymorphism, especially on the particle surface.

In general, API particles size-reduced by WET present a lower surface area, rugosity, and water content; a higher bulk density; and a quicker electrostatic charge dissipation in comparison to powders micronized by JET. Consequently, the WET API particles have the tendency to show higher adhesion to the carrier than cohesion to themselves. Relative to JET particles, however, WET materials show lower adhesion to the carrier surface, probably due to the smoother ‘polished’ API surface with a

smaller number of contact points. These results show that different processing histories can change the powder interfacial properties, namely the tendency to agglomerate and, according to the formulation composition and strategy used, can potentially impact API content uniformity and the powder aerosolization performance.

Another alternative to overcome the constraints discussed previously is to use engineered particles, created from a solution; spray drying has been an enabling technology for most of the platforms described in the literature and/or is commercially available. This technology can produce inhalable particles with controlled particle size, morphology, surface properties, and density by manipulating formulation composition, such as the inclusion of surface-active agents and process parameters. This increased control over the powder properties allows the optimization of the powder aerosolization behavior and dispersability, which potentially allows for reduction of the API dose while maintaining the amount delivered to the target site. Examples of these 'special' particles with several patents protecting their production include Pulmosol and PulmoSpheres technology developed by Nektar Therapeutics, Technosphere by MannKind Corporation, AIR/ARCUS technology by Alkermes, and iSperse from Pulmatrix and Hovione.

PharmTech: The strong cohesion forces can be a challenge when handling the powder during manufacture or when metering and filling a DPI. How do you approach this problem?

Andrade: The vast majority of DPI products address the asthma and chronic obstructive pulmonary disease (COPD) market space. For these indications, API dosages are typically in the microgram range, requiring a bulking agent for metering and handling the product. To address these requirements, the size-reduced APIs are usually blended with an inert coarse carrier, lactose monohydrate being the most commonly used in DPI formulations. The main challenge of lactose ordered mixtures is to balance the cohesion (API–API) and adhesion (API–carrier) forces that are necessary for ensuring a stable and homogeneous blend while enabling good aerosolization efficiencies.

In general, the API has to be adhesive enough to attach to the carrier-surface and to leave the capsule and the device, but not too adhesive, so that the inhalable API is released from the carrier surface upon oral inhalation. Generally, the larger carrier particles impact in the mouth and throat with a significant amount of API still adhered to the surface, while the remaining inhalable API will deposit throughout the lungs; maximizing the latter fraction is obviously the goal of the inhalation drug-product formulator.

The cohesion forces can pose a challenge during the blending step, causing API agglomeration and consequently, producing non-uniform powder blends. A well-developed mixing procedure is, therefore, crucial to ensure blend uniformity and so that you can proceed with product development.

Besides the cohesion and adhesion forces, the electrostatic forces also play an important role during the powder handling, blending, capsule filling, and even powder performance evaluation. All of these manufacturing steps induce electrostatic charging of the powder blend. For this reason, approaches such as the use of anti-static equipment, the control of the environmental humidity, and the establishment of relaxation times to enable electrostatic charge dissipation between each processing step are strongly recommended.

PharmTech: How does the powder mixing process influence agglomerate behavior of the formulation in the DPI?

Andrade: For a successful blending process, we need to provide an adequate balance of energy to the formulation so that the cohesion forces of the API are overcome, enabling a homogeneous drug distribution across the formulation.

By using carriers with different properties in different mixing processes, distinct powder blending, distinct downstream processing, and differential performances can be observed. The results observed, when different mixing processes are used, support one of the two dispersion theories—either the 'filling' of the carrier active-sites hypothesis or the drug/fines agglomerates-formation hypothesis. Whether or not the different addition order, mixing time, and velocity, amongst other factors, can impact the blend uniformity and the final performance will depend on the properties of the API and excipients, as well as on the blending procedure.

One of the challenges of the scale-up of an inhalation product is the transfer of the formulation process from laboratory-scale, where a low-shear mixer is commonly used, to the large-scale formulation, where both a high-shear and a low-shear mixer can be used. The different mixing principles can affect the resulting blending properties and consequently affect the powder aerosolization behavior and thus affect downstream processing and aerosolization performance. In addition, the use of a high-shear mixer can lead to comminution of the lactose carrier, increasing the percentage of fines, which can consequently improve the powder fine particle fraction (FPF)—which is the amount of powder that reaches the deep lung, presenting an aerodynamic particle size distribution below 5 micron—but can hinder the bulk powder flow properties. This can impact the downstream processing as well as change the aerosolization performance previously developed during laboratory-scale. On the other hand, the use of a low-shear mixer can lead to blend homogeneity and content uniformity challenges, which can also affect the downstream processing and product development strategy.

PharmTech: Can you elaborate on the drug–carrier interaction and its relationship with aerodynamic performance of a carrier-based formulation?

Andrade: The API and carrier components and properties in combination with the mixing process, the environmental conditions, and the device/flowrate requirements will determine the aerodynamic performance of the DPI. As previously mentioned, there are two dispersion theories, and according to the carrier properties used and mixing procedures, together with the API cohesion and adhesion forces, different scenarios can be observed.

In general, the increase of one parameter does not always translate to an advantage

for the overall process. A simple example is the incorporation of lactose fines in the DPI formulations; although it is known to increase the powder performance by increasing the FPF, it also affects the downstream operations such as automated capsule-filling rejection rate and the emitted mass consistency. This means that a careful balance should be taken while developing a DPI product, because a composition that favors the FPF can have a deleterious effect on the overall process. Therefore, it becomes important to evaluate trade-offs and, in this way, identify compositions that are able to benefit the process as a whole.

Regarding some of the downstream processes, such as the capsule filling performance, we have observed that a higher fill weight of the capsule benefits the process by reducing the rejection rate. Additionally, the amount of fine particles and their particle size are also major contributors to the rejection rate in the manufacturing/filling process. Lastly, to ensure a robust formulation and guarantee a consistent drug delivery and performance, we need to minimize the process and materials variability, by minimizing the intrinsic batch-to-batch variability from both the API and carrier properties.

PharmTech: How does carrier particle size affect inhalation performance of the powder mixtures?

Andrade: Carrier-based DPI formulation strategies typically consider carrier systems composed of coarse and fine grades of lactose. To improve the FPF, the percentage of fine lactose particles is increased; however, this may also impact negatively on the downstream processing.

Some studies show a strong relationship between the influence of the lactose particle size and the final aerodynamic performance. In some cases, where the drug/carrier agglomeration hypothesis seems to be predominant, the fine lactose particle size seems to be the main contributor for the final powder outcome. These fine lactose particle attributes confer different dispersibility and flow properties, which can enhance or hamper the downstream processes and ultimately the final powder performance.

As a final remark, it is important to point out that each inhalation product has different properties. The formulation and blending process must, therefore, be assessed case by case. That is why a holistic and integrated approach must be taken when evaluating different inhalation drug-product development strategies and carefully integrating the formulation development strategy with the delivery device. Hovione has developed two DPI devices, the two-cavity single-use DPI, TwinCaps, and the capsule-based DPI, XCaps. With our knowledge in both particle engineering, formulation, and their integration with the delivery device, we were able to assist Daiichi-Sankyo in developing the TwinCaps Inavir inhaled product, currently the category market leader in Japan for the treatment of influenza.

Reference

1. BCC Research, Pulmonary Drug Delivery Systems: Technologies and Global Markets [2], accessed Apr. 22, 2015.

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