

Pulmonary Drug Delivery—Particle Engineering for Inhaled Therapeutics

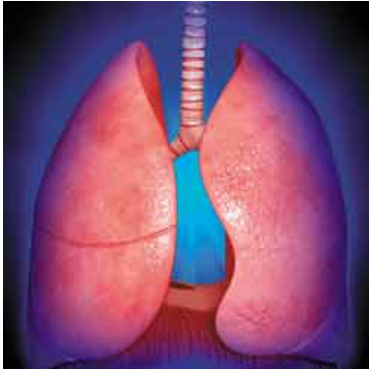
Industry experts discuss the various factors affecting drug delivery to the lungs and key considerations when developing inhalation formulations.

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The pulmonary route is gaining increasing popularity as a fast and effective way of delivering drugs to the lungs both locally and systemically. There are several reasons for this interest, noted Conrad Winters, PhD, director, and Filipe Neves, PhD, group leader, both from the Drug Product Development Group at Hovione. “Firstly, advances in device technology have made inhalation drug delivery more convenient and patient-friendly. Secondly, from a therapeutic angle, the lungs provide a high absorption area with extensive vascularization, leading to rapid delivery of the drug. Moreover, because it circumvents first-pass metabolism, lower doses can be administered compared with the oral route.”

The pharmaceutical industry has now realized that the potential of inhaled therapies goes beyond asthma and chronic obstructive pulmonary disease (COPD), and therefore, offers opportunities for growth and product differentiation. “Pharmaceutical scientists are increasingly using the pulmonary route as an effective mechanism for systemic drug delivery,” observed Gonalo Andrade, PhD, business development manager, Hovione. “The greatest interest appears to be in antibiotic delivery, with two products already approved—Tobi (tobramycin, Novartis) and Cayston (aztreonam, Gilead)—and at least three others in Phase II-III clinical trials (i.e., amikacin, vancomycin, and levofloxacin).”

Another key driver has been the development in the delivery of macromolecules, added Peter Villax, vice-president of Hovione. “While the lungs are highly permeable to small molecules, therapeutic peptides, and proteins (that would be deactivated or are too large for absorption via the oral route) are also extensively absorbed from the lungs. This advantage provides for the delivery of molecules previously only administered via the parenteral route, such as vaccines and gene therapy.”

The three types of devices used for pulmonary drug delivery include nebulizers, pressurized metered-dose inhalers (pMDIs), and dry-powder inhalers (DPIs), explained Peter York, chief scientist, and Lyn Daintree, development director, both at CrystecPharma. “While nebulization is used in cases where pMDIs and DPIs are not appropriate, such as for treating small children or infirm patients, or in severe cases of respiratory disease, pMDIs and DPIs offer distinct advantages for patients, prescribers and manufacturers.”

“Patients are much more willing to be placed on an inhalation product than on an injectable product, especially when it’s self administered. And for that reason, we can expect patient compliance to be better,” said Bill Schachtner, associate director, Small Molecule and Inhalation Product Testing Services, PPD. “Moreover, unlike injectable products, pMDI and DPI products do not require sterile manufacturing or cold-chain storage. In contrast to injectable products, which are often limited in the ability to provide multiple doses due to sterility issues, pMDIs and DPIs are usually designed as multidose products.”

To gain insight into the role of particle engineering in the formulation of inhaled therapeutics, *Pharmaceutical Technology* spoke with Daintree and York (both referred to as CrystecPharma thereafter); Andrade, Neves, Villax, Winters (collectively referred to as Hovione); and Schachtner in a roundtable discussion.

PharmTech: What factors control drug delivery to the lungs?

Hovione: Inhaled drug delivery is different from other types of administration because in addition to biological factors, the function of the inhaler and its interaction with both patient and drug dose are key to delivery success.

The physiology of the lungs is designed to keep particles out of the body. Pulmonary drug delivery must, therefore, overcome these barriers. The epithelium of the respiratory system varies in thickness and corresponding permeability from the comparatively thick trachea to the more permeable alveoli. Hydrophobic molecules can be absorbed through the transcellular pathway of the lipid bilayer around cells. More hydrophilic molecules are subject to paracellular absorption through the aqueous pores in the intercellular tight junctions. Some molecules are also subject to an active transport mechanism. The absorption profile of an inhaled molecule is the culmination of all these routes of absorption.

In terms of the technology, pulmonary drug delivery is determined by the nature of the API, the formulation, the device, and their functional performance in aerosolization. An important feature of inhaled drugs is the particle size of the dose components, particularly the active molecule. Particles that are too large will not reach the deep lung tissue whereas particles that are too small risk being exhaled.

In simple terms, particles between 1 and 5 microns will be deposited in the lungs. A number of particle size-reduction and particle-engineering technologies (e.g., air jet milling, spray drying and wet polishing) can be used to generate particles with aerodynamic particle sizes within this range. The problem is that very small particles have strong cohesive and adhesive forces, and therefore, tend to form agglomerates, which need to be dispersed for effective delivery.

Because the particles are often formulated with coarser lactose, they also need to separate from these carrier particles for correct deposition in the lung.

Developing solutions to these challenges requires close cooperation between the device engineer, the formulator, and the particle engineer. The device expert needs to develop an inhaler that efficiently delivers the dose. For DPIs, inhalation delivery is driven by the patient's inspiratory effort, therefore, the device must efficiently convert this source of energy into effective dispersion forces (to break up the agglomerates, separate particles of active and carrier, and aerosolize the dose) and entrainment forces (to move the aerosol cloud out of the device through the mouth and pharynx into the lungs). The challenge for the engineer is to make sure that this dispersion and entrainment happens in a way that is not affected by changes in inspiratory effort and air flow. In other words, the performance of powder inhalers must be as flow independent as possible, and this is usually done by engineering devices to achieve their peak performance at a low flow rate that most patients will be able to achieve.

As the aerosol cloud leaves the inhaler (i.e., the emitted dose), the device will have dispersed the dose into inhalation-sized particles (i.e., the fine-particle dose). Several factors affect this performance in a complex manner requiring multidisciplinary solutions. For instance, particle adhesion to inhaler surfaces, which affects the emitted dose, can be minimized by choosing the right polymer, followed by engineering of the charge potential of the particles, and finally, by understanding the powder relaxation times needed prior to blending and filling. It is a rather delicate balance that requires a very high level of cooperation between various disciplines.

Schachtner (PPD): Drug delivery to the lungs is affected by many factors between the formulation, device, patient, and disease. The formulation can affect the delivery through the percent drug load, excipient type/amount, and even the manufacturing process to incorporate the drug and excipients. Changing the grade and size of lactose used in a DPI can affect initial blending of the drug with the lactose as well as the ability of the DPI to de-aggregate the drug from the lactose. The use of a lower-pressure propellant for a pMDI can change the ability to adequately disperse the suspended drug when actuated through the same metering valve and actuator orifice.

Device differences can significantly affect delivery given that the selection of a low-versus high-resistance DPI device can alter delivery profiles. At the same time, the use of a high-volume versus low-volume metering valve on a pMDI matched with a large or small orifice size on the actuator can change the product delivery characteristics dramatically. Each of these differences requires formulation and device optimization to deliver the needed amount of medication to the lungs.

With inhalation products also comes the human factor, especially for patient-operated devices. Passive DPI uses the patient's inspiration to pull the drug through the device and de-agglomerate the drug particles from the lactose carrier. The patient's ability to maintain inhalation throughout the process is crucial for proper delivery of the medication. Newer DPI devices in both passive and active designs have been able to overcome some of the issues associated with patient use.

Patient use also is important with pMDI products as the coordination of patient inhalation with actuation of the device will determine whether the proper amount of medication is delivered into the lungs. To address this issue, there are auto-inhalation devices for a limited number of products that are self-actuated once the patient starts to inhale from the device. Additionally, the use of spacers has helped meet the need for paediatric administration where it is difficult to not only coordinate the actuation with inspiration but also to obtain the required attention from a young child.

Of course the severity of the disease also affects the ability to administer the medication properly. The only way to understand its impact on the drug/device system is through proper clinical trials using patients with the target disease state.

PharmTech: What are the key formulation considerations when developing an inhalation drug product?

Schachtner (PPD): The primary consideration in pulmonary drug delivery is generating droplets or particles in the 1-5 micron size range during the patient dosing stage and maintaining that delivery throughout the product shelf-life. For nebulized drug products, the main factor is the solubility and stability of the drug being delivered in an aqueous solution and the nebulizer being used to create the fine droplets being delivered. As with all inhalation products, there are differences between jet nebulizers and the newer vibrating mesh nebulizers in the delivery efficiency and droplet sizes formed.

For a DPI, the ability to create stable, fine particles of the drug will determine the overall formulation development process. Conventional particle size reduction techniques, such as jet milling, works on most of the asthma/COPD drug substances on the market but other particle-generation techniques, such as spray drying, controlled crystallization, or microfluidisers, allow for drug substances that are not amenable to jet milling to be converted to respirable particles.

The particle size-reduction technique used can drive the type of device used as a technology. For example, spray drying can incorporate bulking agents directly into the finished particle, thus, eliminating the need for blending the fine drug substance with excipients such as lactose. These techniques allow for long-term drug-product stability as well as drug dispersion during patient dosing. Lactose blends are the majority of

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currently marketed dry-powder formulations but they require much more energy to disrupt the fine drug-substance particles from the larger lactose particle's surface; therefore, the device to deliver such a blend needs to have incorporated technology for this higher-energy input. Engineered particles, such as spray-dried materials, can create particles that can be readily dispersed without the need for de-aggregation. This allows for a much simpler device on the back end but a higher technical input on the front end of the product development.

pMDIs can work with either solubilized or suspended drug substances depending on the properties of the drug substance being developed. Formulations for water-soluble drug substances are usually developed as suspensions due to the low water content of the hydrofluoroalkane (HFA) propellants used. These formulations can use the same particle size-reduction techniques used for DPIs but will be suspended in a HFA-propellant formulation for dispersion. The delivery of the drug product to the lung is mainly controlled by the incoming particle size of the drug substance; however, other factors such as the propellant, excipients, amount metered from the valve, and actuator orifice size play added roles in the overall final particle size distribution.

For pMDI solution formulations, the solubility of the drug substance is enhanced through the use of cosolvents. Since there are no drug particles to deliver, the delivery to the lung is controlled by the solution formulation (drug content, excipients, cosolvent, propellant type) as well as the amount metered from the valve and actuator orifice size to create droplets containing the medication within the 1–5 micron size range.

For each of these product types, the formulation must show chemical stability. For DPI and pMDI suspension products, these formulations must also maintain physical stability of the fine particles and their delivery from the device.

Hovione: Pulmonary drug delivery is achieved through an understanding of the complex relationship between particle engineering, formulation and device. There are many goals for a formulation scientist when preparing a pulmonary drug-delivery system. First and foremost, the formulation must be stable. Stability has many influences including temperature, humidity, residual solvents, and solid-state form (i.e., amorphous versus crystalline). The bulk powder properties of the formulation can change with time, leading to differences in the dispersivity of the formulation. For a given aerodynamic force generated by the inhaler, an increase in the agglomeration strength of a powder will lead to decreased dispersion and reduced lung deposition.

Another key consideration is the target dose. The target doses may vary widely during the early stages of a development process and different approaches are suited to different dose ranges. Ultralow doses, in the order of a few micrograms, may benefit from a combination approach of composite particles with a conventional lactose carrier. For doses up to 5 mg of active, a carrier-based approach using combinations of coarse and fine lactose is appropriate and widely used. For higher doses, engineered particles that comprise a drug-alone formulation are the preferred path forward.

The inhalation formulation scientist must also consider drug targeting. It may be appropriate to proceed with a unimodal distribution for a mono-directed approach, for example if you are targeting the alveoli, or to proceed with a multimodal distribution for a multitargeting approach. Through control of particle size, it is possible to target different regions of the respiratory tract. Larger particles target the upper airways while smaller particles are required for deep lung delivery.

If blended with lactose, the uniformity of the blended batch is crucial, not just because this is good practice, but also because unit doses tend to be very low, making precise blending even more important. For instance, the smallest dose of Advair formulation contains 50 µg of salmeterol, 100 µg of fluticasone and 12.35 mg of lactose (for a total fill weight of 12.5 mg). The difficulty of getting the right blend is further compounded by the fact that mixing parameters (e.g., time, speed) may also affect the carrier/drug adhesion and thus, the fine-particle dose. Composite particles are not subject to this constraint, hence, their applicability to very low doses. In any case, poor reproducibility needs to be actively addressed at every step of the manufacturing process because the inhaler will itself introduce variability during the delivery of the dose.

From a methodological perspective, developing an inhaled drug formulation starts with the maximization of the emitted dose. Drug material that does not exit the device will not benefit the patient and is a source of variability. Achieving emitted doses in excess of 90% is a development goal. Once a high emitted dose is achieved, the focus turns to maximising the fine-particle dose through the combination of drug particle size, formulation material selection, formulation process control, adequate filling technology and device efficacy. Depending on how these factors are combined and on the drug properties, fine particle fractions of 30% to 80% (in relation to the emitted dose) can be achieved.

Finally, the careful selection of packaging materials ensures minimal change to the formulation over the shelf life, with the balance between cost and protection driving the selection.

PharmTech: Why is particle engineering important in pulmonary drug delivery?

Hovione: Particle engineering has brought a new toolbox to pulmonary drug delivery. These new techniques can induce changes in the material characteristics of the drug and the excipients, modifying size, shape, morphology, and surface, which therefore, have an impact on their delivery characteristics. It is through the application of particle-engineering technologies that we can achieve tailored particles with the appropriate particle size properties designed to achieve maximum lung deposition.

Particle size distribution is only one aspect of the characterization of a particle for pulmonary delivery. A narrow span is desirable not just to improve the targeting and dose reproducibility but also to bring extra IP protection to an old product. Certain particle-engineering approaches can induce changes in the material characteristics, resulting in the generation of amorphous material, particularly in the case of conventional air jet milling and spray drying from a solution. Whether this is intentional or an implicit result of the process, it is important to understand the crystalline/amorphous components, the stability of the system, and whether recrystallization will occur during the shelf life of the product. Particle-engineering technologies applied to particle size reduction can induce changes in surface properties of the particles. Hygroscopicity is an aspect that may change with decreasing particle size. After size reduction, the increased surface area affords for greater water absorption so size-reduced material may behave differently to the starting material. Morphology of the drug substance can affect processing and

pulmonary delivery at many points. A different habit of the starting material will determine how the material mills. Particle size measurements are determinant on the technique used for calculation and prisms and needles can be determined as having equivalent particle sizes but behave quite differently during downstream processing.

Surface chemistry of the drug substance can be greatly influenced by the particle-engineering method. Air jet-mill micronization produces many surface defects and dislocations while microfluidization processes result in smoother surfaces for equivalent sized particles. Surface properties will impact the cohesive and adhesive nature of the engineered materials (regardless of the formulation approach employed) with potential impact on the aerodynamic performance. The surface fractal dimension is a useful value given that geometric details are more important than the bulk picture when addressing particles for pulmonary delivery.

Increasing the surface area enhances the aqueous solubility of materials in accordance with the Noyes-Whitney equation so inhalation size particles can dissolve to a greater extent and faster than those sized for oral delivery, thereby taking advantage of the rapid drug absorption commonly seen with pulmonary delivery.

CrystecPharma: While controlled drug particle size is crucial because of the dimensional challenges posed by the architecture of the airways of the nasal cavity and lungs, other physicochemical characteristics are also extremely important. These include particle morphology and shape, particle surface topography, and charge (or energy), solid-state chemistry (polymorphic form, crystalline or amorphous state), and hygroscopicity. The quality of the final formulation, in terms of the aerosolization performance, physical and chemical stability, dissolution and absorption in the lungs, will be a consequence of an integration of all these contributing factors. This is a complex situation increasingly recognized by pharmaceutical industrial scientists as well as by regulatory authorities who require appropriate data and evidence on these issues to demonstrate the quality, safety and performance of inhaled products presented for approval. The goal is to design and engineer drug particles with preferred and selected physical, chemical, solid state and particle surface characteristics for a specific drug substance to provide optimal aerodynamic performance when formulated or used as a drug-alone system and delivered via an inhaler. Batch-to-batch consistency is also a prerequisite so that data from guiding studies in animal respiratory toxicology and bioavailability, in-vitro aerosolization and dissolution studies can be used in the knowledge that future batches will behave in the same manner.

As for the disadvantages, to a great extent, due to the cumbersome and expensive nature of nebulisers, and in many cases, dependency on a healthcare worker for assistance, wide use of this group of inhalers has been bypassed through the advent of pMDIs and DPIs. For pMDIs, issues were focused until recently on the chemical type of propellants used and related environmental concerns; however, the advent of newer propellants has removed this specific challenge while at the same time leading to formulation challenges in some instances. The limited number of regulatory-approved functional excipients, such as wetting and suspending agents, which are routinely required to ensure efficient in-use performance and uniformity of individual doses on activation of the pMDI, can also be problematic.

PharmTech: What techniques are used in particle engineering for inhalation formulations. Can you tell us the pros and cons of each technology and how they compare with one another?

CrystecPharma: In preparing the necessary fine particle size for drug substances for inhalation medicines, there is almost a total reliance upon a 'top-down' high-energy milling operation--micronization or fluid energy milling. While this established method provides fine-sized material in the respirable range for low molecular weight drug substances, it is well recognized that the uncontrolled breakage of larger particles to smaller particles frequently causes other undesirable effects. Among these effects that have been reported are the generation of small but variable amounts of hygroscopic amorphous domains within a crystalline phase and highly energized and electrostatically charged surfaces. Process yields can be disappointing, especially when processing materials are expensive, or of limited availability, and batch-to-batch variability is frequently observed.

In some cases, it has been reported that it is necessary to 'stabilise' drug powders after milling for a period of time under controlled temperature and humidity to reduce downstream handling and secondary processing challenges as well as minimise problems of diminished chemical and physical stability, especially those related to particle size growth on storage.

It follows from previous comments, together with a forward-look to the likely demands for next-generation inhalable medicines, that alternative and more controlled processes for preparing inhalable-sized particles, for biotech and larger molecular weight drugs as well as the low molecular weight materials, are required.

Over recent years, there have been exciting developments based on a 'bottom-up' approach to preparing the fine-sized particles from drugs in solutions. These processes focus on alternative methods of drying the solution to generate the required inhalable-sized particles without the negative features frequently induced by high-energy milling, and include spray drying, freeze-spray drying, and supercritical fluid (SCF) processing. Perhaps an 'ideal' process can be defined as one that is a single-step operation (i.e., from solution to inhalable drug particle) that can be 'tuned' to produce particles with the desired and targeted size and size distribution, morphology, physicochemical characteristics and related aerodynamic properties. The process and technology should be capable of providing excellent batch-to-batch consistency, delivering high product yield, be financially competitive, be readily scaled under GMP specifications and be suitable for regulatory approval.

Experience and evidence with SCF technologies have indicated that this technology can meet these ideal requirements. Based on an antisolvent principle using supercritical carbon dioxide as the antisolvent and introducing a drug solution to a flow of the antisolvent under supercritical conditions, dry, respirable-sized drug particles form very rapidly, which are retained in and subsequently collected from a particle formation vessel. Particle physical and chemical properties can be tuned by changing the process conditions and the undesirable features frequently seen for micronized material are eliminated. Batches of material with different and tight particle size fractions within the respirable range have been produced, making possible studies for targeting drug particles to different regions of the lungs. The SCF process has also shown to be viable for a range of biotech and larger molecular weight therapeutic agents. The other processing demands of consistency, high yield, facile scale-up, GMP operation and competitive costing have all been demonstrated.

The Levadex MDI product (Allergan) for acute treatment of migraine, is an example of the "new version" of pulmonary drug delivery. The product is expected to be launched following FDA approval this year. SCF technology was chosen, following comparison with other particle-generation approaches, to prepare (at development and for manufacturing GMP scale) dihydroergotamine mesylate drug particles according to an extremely tight physicochemical specification. The MDI device uses a "soft-mist" principle to aid patient compliance. When inhaled, the drug, an off-patent small molecule, is absorbed rapidly from the lungs into the systemic circulation to provide rapid relief for the patient from recognized onset of symptoms of a migraine attack, thereby enabling patients to minimize or avoid a severe event. This product demonstrates the benefits of adopting alternative technologies to create a "new vision" for an old drug and the innovative approach of systemic distribution via absorption using the pulmonary route, in this case, for treating migraine and for drug delivery the lungs for a rapid neurological effect.

Hovione: Commonly used techniques in particle design include emulsion systems, micronization, spray drying, and supercritical antisolvent systems. Other systems, such as wet polishing, use a combination of size-reduction technologies and isolation approaches.

Emulsion-based systems generate solid composite particles of high density with a narrow particle size distribution. They are complex to produce at large scale requiring large quantities of solvents and significant effort in the removal of residual solvents.

Micronization by air-jet milling often produces irregularly shaped, predominantly crystalline particles. It is the established method of size reduction in the pulmonary drug delivery field and is a solvent-free process. The resulting particles are typically cohesive and possibly contain amorphous domains that will crystallise over time, resulting in physicochemical instability of the particle size-reduced material. In this case, conditioning strategies are used to accommodate and account for this instability. The material is typically difficult to disperse and blend due to electrostatic charges generated during the process.

Spray-dried particles are highly tuneable. Low-density and solid higher-density particles can be produced. Crystalline particles are obtained mainly when spray drying is used as an isolation step (isolating dry powders from milled suspensions) while amorphous composite particles are obtained when spray drying solutions in which the drug is dissolved together with excipients. Scale up is not without its challenges but as inhalation APIs are usually very potent, it is normal to have rather small batches ranging from kilos to tens of kilos. Thermal sensitivity precludes the use of spray drying for some materials and it is important to understand the solid state of drug-excipient systems before proceeding with amorphous materials.

Wet polishing is a new category of particle-engineering technologies developed by Hovione, which employs a range of particle-size technologies, using suspensions as well as bottom-up techniques combined with a suitable isolating method, often using spray-drying technology. It is highly tuneable in terms of particle size generation, resulting in median particle sizes with a precision of $\pm 0.1 \mu\text{m}$ and narrow size distribution. Spans of less than 1.0 are achievable and the inclusion of a size classification step in the wet polishing can reduce the span even further. Wet polishing generates highly crystalline particles with low cohesivity. The particles obtained can then be formulated or blended to improve delivery performance.

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