Achieving Optimal Particle Size Distribution in Inhalation Therapy

Inhalation therapy has proven to be an effective method of administering a number of pharmaceuticals for more than a century. However, achieving the optimal particle size for a treatment with particular pharmaceutical formulations has been a troublesome task. This article addresses many of the concerns that medical device manufacturers and their pharmaceutical partners have when attempting to achieve the correct particle size for an inhalation device.

By Bob Bruno

Until recently, aerosols were used primarily to deliver locally-active drugs to the respiratory system as a means of treating asthma, cystic fibrosis, and other respiratory illnesses. During the past few years, significant advances have occurred in the use of inhalation technology for the administration of systemically-active medicines such as insulin.

View of the M-110EH

For systemically-active drugs, the aerosol particles must be small enough to reach the alveolar surface in peripheral areas of the lung. Pharmaceutical companies are currently developing methods for producing aerosolized formulations containing uniform, optimally sized particles.

Benefits of Inhalation Therapy

A principal benefit of inhalation therapy is the rapid onset of action, especially when compared to perorally-ingested medicine (oral dosages). The fast medicinal action produced by inhalation delivery results from the large absorption area of the lung.

For locally acting drugs, the onset of action is immediate. Systemically-active inhaled drugs reach the blood stream quickly, within seconds. Rapid onset of action is especially important for rescue medications (i.e., asthma products), as well as pain medication and time-sensitive therapies, such as insulin. Patients cannot always afford to wait the 15 minutes or longer it often takes for a tablet to make its way though the gastrointestinal tract.

Avoiding the GI tract is another advantage offered through inhalation therapy. Unlike perorally-ingested medicine, inhaled drugs are not subjected to the first-pass metabolism effect that significantly reduces bioavailability. After a drug is swallowed, it is absorbed by the digestive system. The absorbed drug is then carried through the portal vein into the liver. Some drugs are so extensively metabolized by the liver that only a small amount of unaltered drug may enter systemic circulation. Further, stomach contents and variable absorption levels among patients add to the variability of bioavailability of the drug.

In addition to the problems of delayed onset of action and reduced bioavailability, perorally-ingested medicines can also cause undesirable side-effects in the GI tract. In contrast, medicines that are inhaled are better tolerated by the body, and delivery via the respiratory system provides a friendlier chemical environment that is less destructive to the medicine.

Injected drugs also avoid the problems associated with the GI tract, but needles are invasive by definition. In some instances the social environment or physical constraints effecting the patient may make it difficult or socially uncomfortable to effect self injection. Inhaled drugs are perceived as being more user-friendly than injections, resulting in better patient compliance for self-administered medications. Inhalation therapies also provide faster onset of action compared to intramuscular injection.

Effect of Particle Size

The destination of aerosol particles is critical to the efficaciousness of inhalation therapy. For locally-acting drugs, the particles obviously need to be deposited in the area of the respiratory tract requiring treatment. The treatment of asthma, for example, requires that the inhaled drug reach the lower airways in order to achieve the desired therapeutic effect.

For systemically-acting drugs, a high percentage of particles needs to reach the alveoli deep in the periphery of the lung. The lungs contain about 300 million pulmonary alveoli that serve as the primary sites of gas exchange with the blood and are the fastest and most efficient area for absorption of systemically-active drugs.

The extent of deposition of the inhaled particles (as opposed to the portion that is exhaled) and the location of the deposition depends largely on the size of the particles and the velocity of inspiratory flow.

Large particles (5-10 µm) do not follow changes in the direction of air flow and have a tendency to be deposited by inertial impact; therefore, they tend to be deposited

in the upper airways without reaching the site of action or reabsorption. Moreover, particles deposited in the mouth and throat can be swallowed and can lead to local or systemic side effects. This phenomenon is often observed with cortisone asthma medication, which can result in infections in the mouth.Intermediate-sized particles (3-5 µm) can be carried further, into the bifurcations and smaller airways of the bronchii and bronchioles. Small particles (≤3 µm) behave more like gas molecules and follow the airflow all the way to the alveoli.The very smallest particles (<0.5 µm) can fail to be deposited in the alveoli, and portions of the medicine can resultantly be exhaled, therefore not achieving the desired therapeutic levels. Controlling the air velocity by slow inhalation will maximize the number of particles that reach the alveoli and minimize the number that are exhaled.

Formulations

The size of the aerosol particle entering the body is a function of the inhaler device and the formulation of the medication. Inhalers and nebulizers of different types each have the ability to generate aerosol particles of certain size range.

For liquid formulations containing soluble drugs, the size of the aerosol particle is largely a function of the design and operation of the delivery device –the nebulizer or "atomizer" that converts the liquid into a vapor or mist.

However, for drugs in powder form and for insoluble drugs that are suspended or dispersed in emulsions, the particle size in the formulation of the drug product is critical. The formulation of the drug product and the design of the delivery device must be matched in order to produce uniform and optimally sized aerosol particles.

For example, if a pharmaceutical company is formulating liquid medication with suspended drugs and the goal is to deliver aerosol droplets with a mean particle size of 3.0 µm, the component drug suspended inside the liquid droplets must have a particle size smaller than 3.0 µm. Otherwise the droplet would not be able to carry the drug and would remain "empty." Therefore, when formulating liquid inhalation medication with suspended drugs, the size distribution of particles must be carefully adjusted and controlled.

The actual size of the drug particle depends on the type of dispersed system (suspension, emulsion, liposome, or colloidal system). Studies performed by PARI GmbH, a worldwide leader in aerosol delivery and research, clearly indicate that the inhalation efficiency with suspended drug particles will dramatically increase when the drug size falls below 1.0 µm.

Aerosol droplets are typically not uniform in size but rather have a size distribution. In other words, an aerosol with a mean particle size of 3.0 µm will contain some particles larger and smaller than the mean size. The goal is to achieve relatively uniform product with a limited particle size distribution, as represented by a low polydispersity index value or as plotted in a narrow bell curve.

Particle Size Reduction Methods

A number of methods of particle-size reduction have been employed to develop and manufacture dispersed formulations of inhalation medicine. Precipitation,

coacervation, and other emulsion-based methods are employed in research environments, but they can cause chemical reactions and thermal stress that can be harmful to the drugs. Moreover, the solvents and other chemicals used in the process can remain as residue that can be toxic in the lungs. In fact, process chemicals and excipients that are approved for oral medication may not be acceptable for inhalation therapy.

For these reasons, several mechanical methods are frequently used, including conventional homogenization, ultrasonication, and high shear fluid processing.

Conventional Homogenization

Historically, the most common mechanical process for particle-size reduction is the conventional homogenization process. The process was originally designed for processing milk and other dairy products. Auguste Gaulin received a patent in 1899 for a milk homogenization mechanism that reduced the size of fat globules in order to prevent the formation of a cream layer. The process involves forcing milk through a tiny orifice under high pressure.

Over the past century, more than 100 additional patents have been awarded for improvements on Gaulin's original design to produce smaller average particle size and achieve higher levels of precision than traditionally required by the dairy industry. For advanced products, conventional homogenizers can be designed to perform a variety of cell disruption, particle size reduction, and emulsification operations by selecting or creating a particular orifice size and valve geometry and by adjusting the pressure.

However, for conventional homogenizers, the orifice size, valve geometry, and pressure settings apply only to a specific flow rate. When scaling up from a laboratory-size homogenizer to a pilot system, and from a pilot system to a full-scale production system, completely different valves are used and the pressure may need to be raised or lowered considerably. Sometimes several iterations of equipment design must be tested before an acceptable product is produced, or until the specified flowrate is achieved.

Conventional homogenization has served the needs of the dairy industry for over a century. However, particle reduction applications in the pharmaceutical and biotechnology industries require a level of precision, uniformity, and predictability that is usually best achieved with newer particle-reduction technology.

Ultrasonication

Sonic disruptors, or sonicators, break up particles in liquid media with powerful ultrasonic waves, ranging from about 15 to 50 kHz. Ultrasonic waves in these frequencies are inaudible to the human ear, but they are capable of exerting pressures of more than 500 atmospheres and generating temperatures of up to 5,000&#176C. A probe or horn containing a piezoelectric generator amplifies the waves into an intense beam that creates the cutting or shearing effect on particles. This effect is called cavitation.

At a microscopic level, the pressure waves cause bubbles to form and then grow

and collapse violently. This implosion generates a shock wave that reduces particle size. The process is so powerful that it can easily over-process materials, excessively pulverizing the product. The high temperatures can also harm the drug or alter its chemistry. Sonicators are commonly found in the laboratory, but they can be prohibitively expensive for producing commercial production volumes.

High Shear Fluid Processing

A relatively new method of particle reduction –high shear fluid processing –is favored by many research laboratories, as well as pharmaceutical and biotechnology companies, because of its unparalleled ability to produce extremely small particles of uniform size and to scale up linearly from laboratory to production volume.

High shear fluid processing systems contain an electric-hydraulic system providing power to one or two single-acting intensifier pumps. The pump amplifies the hydraulic pressure to the selected level which, in turn, imparts that pressure to the product stream. Process pressures range from 2,500 to 40,000 psi, resulting in high velocity, high shear process streams.

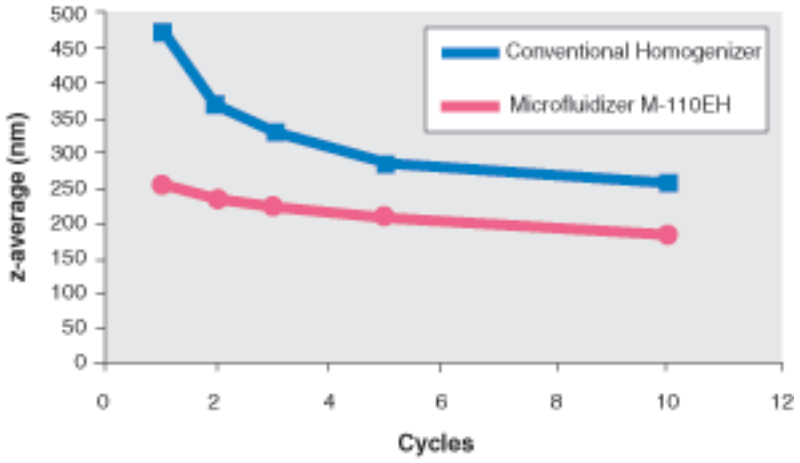
The intensifier pump supplies the desired pressure at a constant rate to the product stream. As the pump travels through its pressure stroke, it drives the product through precisely defined fixed-geometry microchannels within the interaction chamber. At the end of the power stroke, the intensifier pump reverses direction and the new volume of product is drawn in. The intensifier pump again reverses direction and pressurizes the new volume of product, repeating the process.

As a result, the product stream accelerates to high velocities, creating shear rates within the product stream that are orders of magnitude greater than conventional means. The entire product experiences identical processing conditions, producing uniform particle and droplet size reduction.

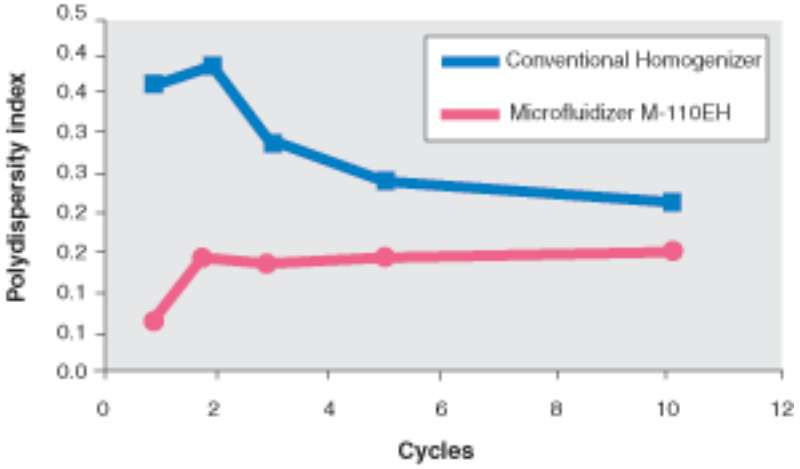
The fixed geometry of the microchannels not only ensures that the processing conditions are identical for all product passing through a single machine, but that the processing conditions are also identical for all machines using a particular interaction chamber design and pressure setting regardless of flowrate capacity. Therefore, once a high shear fluid processor achieves a successful result with a small laboratory system producing only a few hundred milliliters per minute, the same interaction chamber and pressure specifications can be used in the design of a full-scale production system that produces commercial larger volumes. Because of the ability to scale-up production seamlessly, many users of high shear fluid processors skip the usual pilot stage and move directly from the laboratory to full-scale commercial production capacity.

Comparative Testing

PARI GmbH has conducted laboratory testing to evaluate the performance of various particle reduction methods for the formulation of inhalation medicine.



Budesonide in emulsion. Smaller particle size.



Budesonide in emulsion. Narrower size distribution.

The Microfluidizer M-110EH high shear fluid processor, was evaluated in comparison to a conventional homogenizer. In the first set of tests, both pieces of equipment were used to create a suspension formulation of Budesonide –a glucocorticoid steroid used for the treatment of asthma, non-infectious rhinitis (including hay fever and other allergies), and for treatment and prevention of nasal polyposis. The drug also has efficacy for bowel and colon disease, but it has a high first pass metabolism, making it an excellent candidate for systemic inhalation delivery.

In the side-by-side test of the Budesonide suspension formulation, the PARI laboratory found no significant difference in the average size of the particles between the Microfluidizer processor and the conventional homogenizer. However, the Microfluidizer processor produced a better size distribution (e.g., a polydispersity index of 0.8 compared to 1.0 after one cycle).

The difference between the Microfluidizer processor and the conventional homogenizer were more pronounced for the production of emulsions that can be used to deliver Budesonide. With one cycle of processing, the Microfluidizer processor produced a smaller z-average particle size (250 nm) compared to 475 nm for the conventional homogenizer (Figure 1). Moreover, the conventional homogenizer required five cycles to come close to the results achieved by the Microfluidizer processor in a single cycle. The Microfluidizer processor also produced

a dramatically narrower particle size distribution (Figure 2), with a polydispersity index of only 1.3 after one cycle, compared to &gt4.0 for the conventional homogenizer.

The PARI researchers found that high shear fluid processing provides an excellent method of particle-size reduction and production of dispersed system formulations for inhalation therapies. The system offers precise control over processing conditions, and the availability of different homogenization chambers provides flexibility in producing a variety of formulations with various particle sizes while maintaining a very narrow particle size distribution.

ONLINE

For additional information on the technologies and products discussed in this article, visit the following websites:
www.microfluidicscorp.com [1]
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