Nebulisers are often chosen as a delivery mechanism during drug development and are growing in popularity within the biotech industry. A major reason for this is that, for rapid assessment of efficacy, nebulisers overcome some of the issues associated with formulation via other inhalation routes – thereby providing a rapid route to the clinic. Additionally, the simultaneous development of formulation alongside device selection can improve performance and offer a competitive advantage.

**Choice of Delivery Route**

Although injections are well accepted for the delivery of macromolecules for systemic diseases, there is significant interest in the delivery of proteins and
peptides via the inhaled route. Nebulisers create a
mist of medicine that can be inhaled passively, and
the pulmonary route provides many benefits for
biotech drug delivery. The alveolar epithelium that
lines the lungs naturally absorbs proteins and
peptides without enhancers, and offers an enormous
surface area for the absorption of compounds. In
addition, pulmonary delivery can provide a rapid
onset of action.

Proteins and peptides are typically digested by the
gastrointestinal (GI) system, and so if drugs are delivered
orally, a large dose may be required to achieve
therapeutic levels. Also, most macromolecules do not
pass readily through the skin or mucus membranes and
so are not suitable for transdermal patches.

So, the nebuliser route offers advantages over oral,
intranasal and transdermal alternatives.
Off-the-Shelf Versus Bespoke

Until recently nebulisers had been classified as medical devices – rather than ‘integrated products’ like dry-powder and metered-dose inhalers – because they could be used with a variety of drug formulations. So using an off-the-shelf device and optimising the performance of a formulation enables a product to progress quickly to the next stage of development.

However, this is changing with the publication of the new standard, ISO 27427:2010, that specifies more stringent requirements for the “safety, performance and testing of general purpose nebulising systems that are intended for continuous or breath-actuated delivery of liquids, in an aerosol form.”

While the lowest-cost option is to use a generic device, many larger pharmaceutical companies are developing their own devices in parallel with the product; this may have the advantage of being multi-dose and thus harder for others to copy.

These factors have resulted in an increased focus on the need to optimise nebuliser performance as part of the formulation development process.

Formulation Process

As a product progresses through the development pipeline, extra work will be required to ensure the suitability of a formulation for each stage of development. Screening at an early stage should be ‘fit for purpose’ – but while investment in this stage can prevent more costly mistakes later on, as well as provide data that can add value to the product, this can be a wasted effort if the product fails later in clinical trials.

By performing the appropriate amount of work at the right time, it is possible to ensure the cost-effective use of resources, and balance the work required with the business objectives.

Solution or Suspension?

The focus of development should be to find suitable formulations that can aid product stability and selection of delivery vehicle, as well as ensuring that the activity of the molecule is not adversely affected in the final form. The major challenge is how to deliver fragile biomolecules without damaging them.

With a nebuliser, a drug can be delivered either as a solution or a suspension. Solutions have the advantage that they are easier to develop than suspensions and often require only a saline solution and buffers. However, suspensions are often more stable than solutions.

Pre-formulation and characterisation studies of the molecule are used to guide the formulation process. For example, while hydrophilic peptides and those with fewer than five amino acids are generally soluble in aqueous media, many peptides under development are poorly soluble. A rapid screening platform can accelerate this process and identify formulations that are less inclined to degrade or denature over time.

Testing for Aerodynamic Particle Size

For nebulised products, the size of the droplet is important in determining where in the lungs the drug will be deposited. A common source of confusion when discussing nebulised products is the difference between a particle and a droplet. A particle is a solid, and may be held within a liquid droplet.

In solutions, the molecule is evenly distributed, and so droplets of the same size will contain the same amount of drug. This is in contrast to suspensions, where the size and concentration of the particle(s) within each droplet may vary. It is possible to alter the particle size through micronisation and other techniques if required.

For a drug in suspension, where the particles may not be evenly distributed between droplets, the aerodynamic
particle distribution must be determined using a next generation impactor (NGI, see Figure 2, page 28). However, this test is time-consuming to perform and analyse, making it relatively expensive to use.

For a homogeneous solution, however, there is a correlation between droplet size and aerodynamic particle size – and so laser diffraction can be used. Here the spray is passed through a laser beam, and the angular intensity of the scattered light is measured. The scattering pattern is then analysed using an optical model to produce a size distribution; this determines the size of the droplets, but does not measure the drug content itself.

Laser diffraction analysis not only provides a droplet size distribution, but also a time-history plot that gives information on how the nebulised formulation behaves throughout the duration of the nebulisation process. In addition, the results are available immediately and so different formulation variants can be screened very rapidly. This accelerates development times – making laser diffraction a valuable tool in the early stages of product development.

Just as the droplet size and aerodynamic behaviour of the formulation are of critical importance, so too are the total amount of drug delivered to the patient and the rate of delivery. This can be assessed using a breath-simulating pump to replicate tidal breathing. The regulatory guidelines have recently been updated, and now incorporate neonatal and infant breath profiles, in addition to the adult profiles already covered.

Improving Nebuliser Design

Throughout the development process, the amount of drug needs to be accurately delivered, and there are a number of new nebuliser designs emerging that can help increase this accuracy. A disadvantage of traditional nebulisers that deliver the drug as an aerosol is that the dose is dependent on the patient’s breathing pattern – and so it can be variable.

Recently, however, there has been increased interest in formulation using controlled-dose nebulisers. These use a vibrating mesh technology, and can deliver a drug during the first 80 per cent of the in-breath – the time over which the drug is deposited in the lungs. This is extremely valuable for accurate dose-range studies and so for small-scale trials can offer considerable advantages. These nebulisers are also less likely to damage more fragile compounds.

Conclusion

As more accuracy is being demanded of nebuliser devices, increased attention is being given to the role of formulation in improving drug delivery and also to the technologies that are available for testing.

Additionally, new types of device are emerging; in the case of some of the most fragile biopharmaceutical products, for example, the use of controlled-dose nebulisers to administer an exact dose has proved beneficial.

We have found that an integrated approach to formulation and analysis is driving further innovation in this exciting area of drug delivery.