

Lung Power

Mark Copley of Copley Scientific discusses the development of systems for inhaled drug delivery, and examines the benefits of the pulmonary route

The technologies underpinning inhaled drug delivery have developed rapidly over the past decade as the pharmaceutical industry has moved to exploit the lungs as a route to rapidly introducing therapeutics into the body. Many locally acting and systemic drugs are now routinely delivered in this way. However, developing delivery devices and formulations that perform well is challenging, and is an area of continuing investment for the industry.

It seems timely, therefore, to review the evolution of delivery devices and the benefits provided by different designs as a prelude to considering key performance targets for inhalation systems and the *in vitro* analytical techniques used to ensure they are met.

INHALATION DEVICES

Inhalation systems were originally introduced to deliver locally acting drugs to the lung. Treatments for asthma and chronic pulmonary obstructive disease were some of the earliest commercialised products, and remain key areas of use for the technology. However, the lungs also offer a massive

surface area for the rapid absorption of systemically acting drugs. Inhalation has a high degree of user acceptance and is particularly useful for treatments that cannot survive the gastrointestinal route.

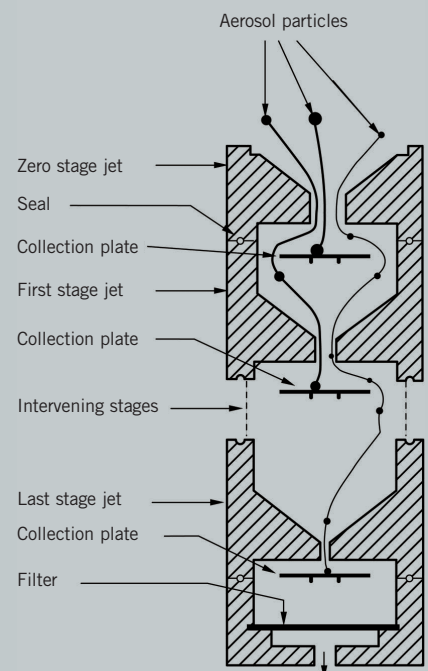
As the use of pulmonary delivery has increased, new devices have been brought to market, and today there is a broad range available. Collectively described as orally inhaled and nasal drug products (OINDPs), these devices can be classified under the following headings:

- Pressurised metered dose inhalers (pMDIs)
- Dry powder inhalers (DPIs)
- Nebulisers
- Nasal sprays
- Aqueous droplet inhalers (ADIs)

Key differences between the devices are whether the delivered dose is: wet (in suspension or solution form) or dry; pre-metered or controlled by usage; and the extent to which delivery is coordinated with inhalation. MDIs (or pMDIs) are the most commonly used of the delivery

devices. Pressing down on the MDI canister within the actuator releases an aerosol cloud, produced from a fixed volume of liquid formulation. MDIs are small, convenient, inexpensive and particularly suitable for the

Figure 1: Schematic of a cascade impactor



bronchodilators and corticosteroids used to treat respiratory illness.

However, two significant drawbacks to the MDI have spurred the development of alternatives. Firstly, with a conventional MDI, there is no coordination between inhalation and release of the dose; this can present problems for young, elderly and chronically ill patients. Spacers (or holding chambers) largely overcome this problem, although in many cases they can be cumbersome to use. Secondly, the propellants (CFCs) with which many MDIs were originally formulated are now banned under the Montreal Protocol (except in some developing nations), leaving manufacturers with a choice between reformulating with an alternative (such as HFA 134a or 227), which is often not straightforward, or developing a new device.

One response has been a renewed interest in DPIs, particularly in Europe, where estimates suggest they will account for 50 per cent of the market by 2012 (1). Manufacturers usually formulate DPIs with an excipient in order to give a dry powder with the required flow and dispersion properties. During aerosolisation, the active is stripped from the excipient and drawn into the lungs, while the remainder of the drug is ingested.

With a traditional DPI, the motive force for aerosolisation is patient inspiration, thus coordinating inhalation and delivery. Active devices also exist to coordinate dose release

with inhalation when the pressure drop generated by the patient reaches the required level. Dry systems are appealing from the point of view of sterility and stability, and the pharmaceutical industry has a long history of powder processing (primarily for tablet production). However, these advantages are countered by higher production costs, and the inhalation strength required to deliver and aerosolise the dose adequately and consistently.

Nebulisers and ADIs both avoid the problems that certain users may encounter with DPIs and MDIs. Nebulisers continuously aerosolise a liquid formulation so that the volume of drug delivered is determined by breathing pattern and period of use. New mesh technology, which uses ultrasonics to generate droplets that are then pushed through a mesh or plate, gives more closely controlled aerosolisation characteristics, and enables the production of smaller, quieter devices. Compared with traditional nebulisers, which are large and mains-powered, these are much more portable, allowing wider use for more applications. Nebulisers are used extensively both in the home and in hospital, particularly with physically weak or older patients.

ADIs are typically a hybrid between a MDI and nebuliser, bringing together the advantages of both technologies to reduce the problem of synchronising inhalation and drug delivery. This is done by releasing the pre-metered dose over a much longer period than a standard MDI. With an ADI, a 'softer' droplet cloud is produced in a highly controlled way using active aerosol generation (mechanical or electromechanical). Such devices deliver a high fine particle fraction and improve reproducibility in terms of patient-to-patient dosing. However they tend to be considerably more expensive than traditional MDIs.

Like inhalers, nasal sprays can also be liquid or powder-based, and are being used increasingly for systemic drug delivery. The nasal cavity and olfactory region present large surface areas for absorption, and are particularly good for the delivery of drugs acting on the central nervous system. Multi- or unit-dose systems are available, and delivery may be manual (hand pump) or propellant-driven.

Development continues, with innovation clearly focused on overcoming the acknowledged limitations of conventional designs. Breath triggering is used increasingly to synchronise drug release

and inhalation in MDIs and nebulisers, while 'active' DPIs incorporate mechanisms that assist powder propulsion. A promising innovation in nasal sprays is the bi-directional device. These use the body's natural reaction to exhalation to prevent fine particles being drawn into the lungs. The overall goal remains the development of user-friendly, patient-compliant devices that are cheap to produce, deliver a high particle fraction and have highly reproducible delivery characteristics.

CONTROLLING DRUG DELIVERY

The consistency of drug delivery is, of course, the defining performance characteristic of an inhalation system. The device must deliver the same amount of active ingredient each time it is used, and this must deposit in the same way, *in vivo*, to ensure consistent uptake within the respiratory system. Delivered dose uniformity can be verified relatively easily by measuring the amount of formulation released each time the device is fired under normal usage conditions (2). More sophisticated testing is required for the *in vitro* investigation of deposition behaviour, which is generally used as a quality control tool to ensure product consistency with that used in clinical trials.

The dynamics of particle deposition in the respiratory system are strongly dependent on particle size. For delivery to the lungs, one to five microns is generally accepted as a suitable size range – larger particles tend to deposit in the upper airways, while smaller particles are easily exhaled. For nasal sprays, the target size range is much larger, typically 20 to 200 microns, but formulators must still pay close attention to the sub-10 micron fraction, since these particles may be inadvertently drawn into the lungs.

For this reason, the regulatory authorities specify aerodynamic particle size measurement in combination with delivered dose uniformity testing for inhalation product characterisation. Cascade impaction is the recommended technique.

UNDERSTANDING CASCADE IMPACTION

The analytical technique of cascade impaction has features that make it uniquely suited for characterising OINDPs (see Figure 1, page 92):

- It measures aerodynamic particle size – the parameter that most closely reflects deposition behaviour

The regulatory framework for OINDPs

It is now widely recognised that the aerosolisation/dispersion performance of all inhaled drug delivery devices is closely dependent on the physical properties of the formulation being used. The implication of this is that drug-specific testing is always necessary. The FDA and EMEA are responsible for inhaler product testing in the US and Europe respectively. Generally speaking, their guidance recommends delivered dose and aerodynamic particle size measurement for all new products (device-drug combinations), although nebulisers remain something of an anomaly. Historically, the drug-nebuliser combination used by a patient has been specified by the prescribing clinician. Nebulisers were developed for 'general' use and were treated as medical devices rather than inhalation products. As of 2006, the EMEA and Health Canada no longer take this approach in their guidance, thus harmonising testing. There is as yet no corresponding guidance in the US, but it is clear that here too the authorities are increasingly specifying that nebuliser and formulation should be tested together.

For all OINDPs, regulation provided by the EMEA and the FDA is supplemented by guidance from bodies such as the European Standardisation Committee and the International Standards Organisation. All of these requirements are translated into practical methods for routine testing in the pharmacopoeias, principally the US and European Pharmacopoeias.

- It divides a sample into fractions, allowing chemical assessment of active content as a function of particle size
- It is ideal for the sub-10 micron size range

All impactors consist of a number of stages through which sample-laden air is drawn using a vacuum pump, with a control valve setting the flow rate. Each stage has a number of closely specified nozzles. Since nozzle diameter decreases at each successive stage, air velocity increases, giving particles progressively more inertia. Particles with sufficient inertia have an impact on a collection surface beneath the nozzles; those with less inertia remain entrained in the air and are carried through to the next stage. As inertia is a function of velocity and particle size, the technique divides the sample into size-based fractions. The size of particles that collect on each stage (the stage cut-off diameter) is a function of both nozzle diameter and air flow rate through the instrument.

Analysing these fractions, typically by high performance liquid chromatography (HPLC), reveals the likely deposition profile of the active. Fine particle dose (FPD) or fraction (FPF) is a key parameter. FPD is usually defined as the amount of active material below five microns in diameter (although this may vary depending on the product), that is to say the amount of material that is likely to deposit in the lungs. FPF is this figure expressed as a fraction of the delivered dose (which excludes any drug that remains on the device mouthpiece itself). Other terms used to assist in characterising the dose are geometric standard deviation (GSD) and mass median aerodynamic diameter (MMAD), which aim to summarise the typically log-normal distributions generated.

Cascade impaction is a precision technique; the regulators and pharmacopoeias specify in detail the methodology used to establish a reliable testing protocol for each new product. Critical issues that must be addressed include:

Air Flow Rate

Air flow rate has a direct impact on stage cut-off diameter, thus it must be set appropriately for the device and should remain constant throughout the test. Leak testing is essential to ensure that flow is the same through all stages. For DPIs, which are especially flow-sensitive, it is also

recommended that a state of critical flow is achieved across the flow control valve downstream of the impactor, to promote stable flow.

The impact of air flow on stage cut-off diameter is most clearly defined for the Next Generation Impactor (NGI) which has rigorously calibrated performance in the range of 15 to 100L per minute (3,4). The performance of the Andersen Cascade Impactor is well documented at 28.3, 60 and 90L per minute.

Instrument Maintenance

As precision instruments, cascade impactors must be well-maintained to ensure optimal performance. Routine checks for signs of wear, tear and corrosion are good practice, while regular stage mensuration verifies that the instrument remains within the specified dimensional tolerances. Stage mensuration is the systematic measurement of all the critical dimensions of the instrument and is normally performed using an optical vision inspection system (5).

Sample Work-Up

To ensure the validity of results, a very high proportion of the delivered dose must be recovered during sample work-up. The regulators specify mass balance tolerances, which are typically met by washing all surfaces within the instrument that have significant drug deposits. A sufficient number of doses should be fired into the impactor during testing, to allow for accurate detection of the active at the work-up stage.

Re-Entrainment/Collection Surface Coating

Particles that rebound from the collection surface will be captured at the wrong stage, compromising data integrity. Collection surface coating reduces this problem and should be considered during method development, particularly for DPIs. Glycerol or silicone oil dispersed in a volatile solvent, which then evaporates to leave a thin film, is most often used.

CONCLUSION

Inhaled drug delivery presents significant challenges to the industry, but the core benefits of using the pulmonary route are clear. Devices must provide consistent delivery of the active in a way that ensures reproducible uptake by the respiratory system. Equally important factors are ease of use and cost of production. Delivered dose and aerodynamic particle size measurement

are key testing methodologies for inhalation systems, providing characterisation data that is essential for optimising the product.

References

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About the author



Mark Copley graduated from the University of Bath, UK in 2000 with a Masters Degree in Aerospace Engineering. For

the past nine years he has been sales manager and product specialist for Copley Scientific's range of inhaler testing equipment and is now Sales Director for the company. Mark is considered a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulisers and nasal sprays. He also provides application support and consultancy, and runs focused training courses and workshops for the inhaled drug testing sector of the pharmaceutical industry. An invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team, Mark has also made contributions to the Inhalanda working group, leading to subsequent revisions to Ph Eur and USP monographs.

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