

Nebulisers: Understanding the Regulatory Framework and Testing Requirements

Nebulisers are a popular choice for inhaled drug delivery, most especially for those with poor coordination or lung function, such as geriatric or paediatric patients. In countries such as China, they represent as much as 36 per cent of the market share for orally inhaled products¹. In this article, author provides an introduction to nebulisers, focusing on the regulatory guidance that governs their development, and the tests required to characterise performance.

Nebulisers are used routinely for inhaled drug delivery both in hospitals and at home. Once loaded, a nebuliser continuously aerosolises a liquid formulation which the patient inhales by breathing through a face mask or mouthpiece. This means that nebulisers, unlike other orally inhaled products (OIPs), do not require the coordination of inhalation with device actuation, making them especially suitable for those with poor coordination or lung function, such as geriatric or paediatric patients. They are also useful for delivering high drug doses over long periods of time. However, because of the mode of action of a nebuliser the amount of drug received by the patient is dictated by their breathing profile.

Here we examine how nebulisers work and how this governs the way in which they are tested. A review of regulatory guidance and of the pharmacopoeia monographs relating to nebulisers, which were revised in 2012^{2,3}, supports a detailed discussion of the specific requirements for dose delivery testing and aerodynamic particle size distribution (APSD) measurement for this important class of OIPs.

How do Nebulisers Work?

Drugs destined for delivery via a nebuliser are formulated as therapeutic solutions or suspensions, which are generally loaded into the nebuliser from a nebule. The nebuliser actively atomises the liquid to form a cloud of respirable droplets using one of a number of different atomisation technologies. Jet actuated systems, for example, use compressed air to achieve atomisation while ultrasonic nebulisers aerosolise formulations by transmitting vibrations from a piezoelectric crystal through the formulation reservoir. These vibrations create a series of waves from which droplets separate to form a respirable

mist. Ultrasonic devices need an electricity supply, which can be a limitation in certain instances, while jet based nebulisers rely on the availability of a compressed air source. Both technologies result in nebulisers that can be quite bulky, and that consequently lack the portability and convenience associated with conventional inhalers. Furthermore, in the case of jet nebulisers, these can be quite noisy due to the need for an associated compressor.

The more recent development of mesh technology has brought portable, silent, battery operated nebulisers to the marketplace. With a mesh nebulizer, droplets are produced by pushing the formulation through a static or vibrating plate, mesh or membrane, using either a vibrating piezoelectric crystal, as in ultrasonic devices, or a vibrating metal head. This technology leads to a very tightly controlled droplet size distribution, offering improved drug delivery characteristics. However, it shares with other nebuliser technology the disadvantage of being costly compared with alternative OIPs.

In use, nebulisers, unlike metered dose inhalers (MDIs) or dry powder inhalers (DPIs), do not deliver a pre-metered dose. Rather nebulisers continuously produce a steady stream of aerosolized droplets, which in some devices is moderated by breath actuation or breath enhancement mechanisms⁴. The amount of drug that the patient receives is, therefore, dependent on how effectively the repetitive tidal breathing cycle of the patient draws this aerosol into the lungs, and the duration that the device is used for.

A Revised Regulatory Framework

Traditionally health care practitioners and hospitals purchased nebulisers and used them with a range of different formulations.



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Breathing Simulator Specification for Nebuliser Characterisation Tests				
	Adult	Neonatal	Infant	Child
Total Volume	500 ml	25 ml	50 ml	155 ml
Frequency	15 cycles/min	40 cycles/min	30 cycles/min	125 cycles/min
Waveform	Sinusoidal	Sinusoidal	Sinusoidal	Sinusoidal
I/E Ratio	1:1	1:3	1:3	1:2

Table 1: The breathing profiles defined for delivered dose testing for nebulisers.

The regulatory framework classified nebulisers as stand alone medical devices leaving the choice of formulation/nebuliser combination as the responsibility of the prescribing clinician. In line with this classification nebulisers were tested in accordance with the European Committee for Standardisation (CEN) Standard for Respiratory Therapy Equipment EN 13544-1⁵.

However, in 2006, new regulatory guidance was issued by the European Medicines Agency (EMA) and Health Canada⁶. This guidance reflected the dependency of safe nebuliser use on the selected formulation/device combination. Inter-brand variability is a known issue with regard to nebuliser performance, but the physical properties of a formulation also impact the droplet size delivered by any individual device. The revised regulatory framework harmonised nebuliser testing with testing for other OIPs, which are consistently treated as combination (device/formulation) products, and is now supported by two new harmonised monographs Ph. Eur. 2.9.44 and USP 1601^{2,3}. These came into force in January 2012 and August 2012 and specify tests for assessing dose delivery and for APSD measurement.

The new monographs provide more comprehensive methods for evaluating nebuliser performance than the standards that predate them, and make use of the most up-to-date testing equipment. However, the preceding standards remain in place. Adherence to the revised regulations and pharmacopoeial methods is consistent with the requirements of EN 13544-1, but there is also a standard from the International

Standards Organisation (ISO) to consider⁷, which incorporates, in most cases, the requirements of its European counterpart.

Delivered Dose Testing

Delivered dose testing is carried out to determine the total amount of drug that the patient might be expected to receive during a treatment period. Two discrete metrics are defined and measured: the active substance delivery rate and the total active substance delivered. Reflecting the mode of operation of nebulisers, delivered dose testing is carried out using well-defined breathing profiles for specific patient types (see Table 1). The defined profiles for child, infant and neonate patients are based on significantly smaller volumes, higher breathing frequencies and different inhalation/exhalation ratios. These are derived from published clinical work and further harmonised with breathing profiles used in a Canadian Standard for the testing of MDIs with spacers and Valved Holding Chambers (VHCs)⁸. Breathing simulators are used to reliably apply these test conditions.

To measure active substance delivery rate the output from the nebuliser is captured on a filter, under appropriate test conditions, over a specified time (typically 60 seconds). Longer test times are applied to provide sufficient mass (greater than the limit of quantification) for reliable analysis, where delivery rates are low. Replacing the filter and continuing the test until nebulisation stops, because the reservoir is empty, enables calculation of the second metric – total active substance delivered. This is the total mass collected during steps 1 and 2 of the test.

Breathing simulators, exemplified by the BRS Breathing Simulator range from Copley Scientific, have been specifically developed to streamline nebuliser testing in line with the revised monographs. Such systems enable the user to vary:

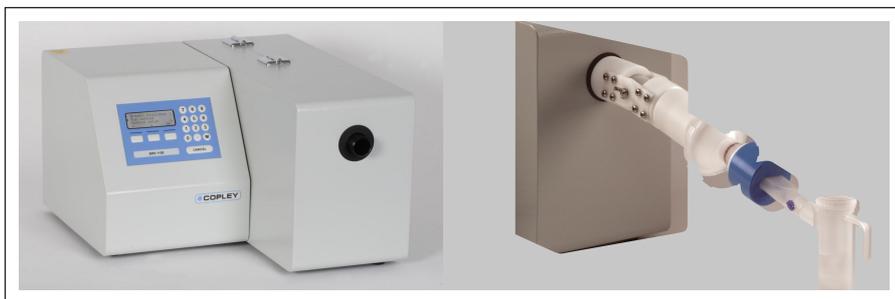
- tidal volume
- frequency
- test duration
- inhalation/exhalation ratio

to easily and accurately apply the test conditions specified for different patient groups.

Measuring Delivered Droplet Size

For all OIPs, APSD is measured to infer information about the likely deposition site of the delivered drug, in vivo. Generally speaking a particle size range of < 5 microns is taken as being optimal for pulmonary deposition. Cascade impaction is the preferred method for APSD measurement because of its ability to provide well-resolved, drug specific particle size data in the size range of interest. Furthermore cascade impaction determines aerodynamic particle size, as opposed to geometric particle size; an intuitively representative metric for OIP characterisation.

During cascade impaction testing, sample laden air is drawn through a series of stages each of which has a defined number of nozzles, manufactured to a closely specified diameter. With increasing stage number, total nozzle area decreases, leading to a progressive increase in particle velocity. At each stage, particles with sufficient inertia impact on a collection surface beneath the stage, while those with less inertia remain entrained in the



The BRS1100 (Copley Scientific) breathing simulator is capable of applying all of the breathing profiles detailed in the new monographs for nebulisers, during routine delivered dose testing.

air stream and flow to the next stage. In this way the sample is size fractionated; chemical (or gravimetric) analysis of the amount of drug collected on each surface then allows full characterisation of the inhaled dose⁹.

Cascade impactors are precision instruments that operate under constant flow rate. The new pharmacopoeial monographs specify a flow rate of 15 L/min – the mid-inhalation flow rate of an adult – as does EN 13544-1. However, at the time of publication of the CEN standard no cascade impactors were commercially available with calibrated performance at 15L/min and so a Marple 298X cascade impactor was typically used, despite a 2 L/min calibrated flow rate (resulting in the need for partial sampling of the aerosol) and capacity limitations. This situation changed in 2004 when the Next Generation Impactor (NGI) was calibrated at this flow rate¹⁰.

The new monographs reflect the suitability of the NGI for nebuliser testing, not least due to the high capacity of its collection cups, and focus specifically on its use. Test methods directly address, for example, the issue of the high thermal mass of the NGI which is recognised as having the potential to impact the accuracy of the reported APSD, by causing droplet evaporation, under ambient test conditions¹¹. Cooling of the NGI prior to testing (especially for drug in solution) is therefore specified unless method development has indicated that this is unnecessary.

In Conclusion

The regulatory framework and pharmacopoeia monographs for nebulisers have changed considerably over the last decade. All OIPs now share a harmonised approach to testing based on the characterisation of a specific formulation/device. Furthermore, the tests specified for nebuliser testing now robustly scope their performance for specific patient groups. Nebulisers are an important class of OIPs for the treatment of paediatric patients and there is now an established testing approach to characterise their performance for such applications.



The NGI has calibrated performance at 15 L/min and high capacity collection cups making it particularly suitable for the characterisation of nebulisers.

The revisions to nebuliser testing have capitalised on recent advances in inhaler testing equipment and prompted further development. The focus on the NGI for APSD measurement, for example, reflects the instrument's suitability for this application which is underpinned by calibrated performance at 15 L/min. The need for flexible, cost-efficient breathing

simulators that enable application of the test conditions set out in the monographs is now met by systems that have been brought to market specifically to meet this need. All the elements required for safe, accurate, and effective nebuliser testing are now securely in place to support on-going development. ■

References

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