

Nebulizer testing

Exploring the implications of new regulatory guidance for testing nebulizers

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Because nebulizers historically have worked with any drug formulation designed for nebulization, regulatory agencies have had a tendency to classify them as medical devices for testing purposes. As a result, the regulatory approach has differed from that applied to other inhalation products such as DPIs and MDIs, with no requirement for drug specific testing with nebulizers. This remains, to some extent, the case in the US where regulation falls under the auspices of the Center for Devices and Radiological Health (CDRH), part of the FDA, and new devices require a 510(k) premarket notification [1]; but regulatory authorities around the world are increasingly linking the approval of formulation and device.

Whereas dry powder and metered dose inhalers (DPIs and MDIs) have always been marketed with drugs as integrated products, until recently most nebulizers were supplied separately from drugs, and prescribing clinicians could select from a variety of drugs to use with any of the devices. Because these devices operate continuously once loaded and require little or no coordination on the part of the user, they have proven particularly suitable for weak, pediatric, or geriatric patients. Nebulizers enjoy wide use both in the home and in hospitals to deliver many different drugs.

Conventional nebulizer designs, however, have a number of disadvantages. For one thing, they either require a supply of compressed air to operate jet technology that atomizes the liquid, or they need a source of electricity for ultrasonic aerosolization, seriously limiting their portability. Other disadvantages associated with conventional devices include their relatively large size, weight, inefficiency, and inter-brand variability. New mesh technology that forms droplets with a closely controlled particle size by pushing the formulation through a static or vibrating plate, mesh, or membrane addresses many of these issues and has led to the development of

portable, silent, battery-operated devices with improved delivery characteristics.

Two major factors affect drug delivery with nebulizers: usage time and droplet size. Unlike other inhalation devices, nebulizers provide continuous delivery instead of a pre-metered dose of drug. Once loaded and activated, a nebulizer operates with the user breathing normally so that the patient's breathing profile and usage time determine the amount of drug received. As with other inhalation products, nebulizers must produce droplets small enough to penetrate into the lungs instead of depositing in the oropharynx, and droplets must be large enough to avoid being exhaled in order to ensure effective drug delivery.

Since nebulizers convert therapeutic liquids into aerosol droplets for inhalation, the drug-nebulizer combination is particularly important because the physical properties of the formulation influence aerosolization behavior and therefore droplet size. In most cases, delivery to the lungs requires a droplet size of around 1-5 μm , although, for deep lung penetration, particularly in children, the target upper limit may be lower, closer to 3 μm [2,3]. In addition, performance can vary significantly from device to device, which is especially true as new nebulizer technology comes to market

While developing and marketing a nebulizer for delivery of a range of formulations remains possible, this approach is becoming less common. Health Canada and EMEA issued new guidance for Europe and Canada late in 2006, and the "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" [4,5] outlines a harmonized approach consistent with that used for other inhalation products, specifying drug-device testing for the majority of products.

The new regulatory guidance emphasizes delivered dose and aerodynamic particle size measurement as the primary characterization techniques for nebulizers but also specifies a range of other factors for consideration, including:

- Physical characterization of the formulation
- Minimum fill justification
- Shaking requirements
- Compatibility with diluent and/or co-administered drugs

- Testing for the presence of extractables/leachables

The new emphasis on assessing the potential for leachable/extractable constituents to migrate from components in contact with the formulation to the stored liquid is a direct result of the increased focus on testing the device and formulation in tandem.

To date, the European Committee for Standardisation (CEN) Standard for Respiratory Therapy Equipment—EN 13544-1 [2] has governed testing of “general purpose” nebulizers, a standard that remains in place. A new ISO standard currently in draft, ISO 27427 [6], based largely on the content of the CEN standard, is expected to be in force before the end of 2008. The new Health Canada and EMEA regulatory guidance is consistent with both of these standards.

In addition to ISO 27427, which will apply to all of these countries, the currently in force regulations pertinent to Europe, Canada, and the US are:

- Europe EN 13544-1
- Guideline on the pharmaceutical Quality of Inhalation and Nasal Products, Health Canada/EMEA
- Canada Guideline on the pharmaceutical Quality of Inhalation and Nasal Products, Health Canada/EMEA
- US 510K premarket notification (FDA90-4158)

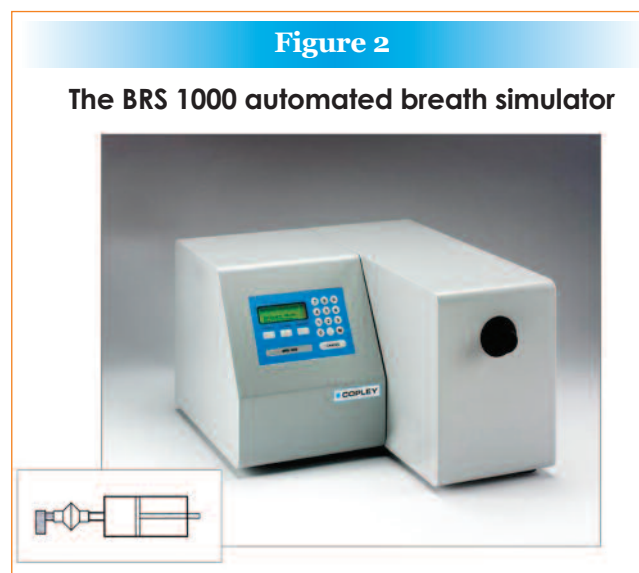
Recognizing the lack of suitable test methods for nebulizers, the US and European Pharmacopoeias have also proposed a new monograph for the characterization of nebulizer preparations [7,8]. The new monograph provides methods for determining active substance delivery rate and total active substance delivered, parameters that characterize delivered dose. The Next Generation Impactor (NGI) (Figure 1), which was commercialized after the establishment of EN 13544-1, is recommended for routine testing of aerodynamic particle size measurement.



Delivered dose testing

The new monograph recommends using a breath simulator (Figure 2) for delivered dose testing, reflecting the routine operation of a nebulizer, with the suggested breathing profile mimicking that of an adult and set at:

- Tidal volume—500 ml
- Frequency—15 breaths per minute
- Waveform—sinusoidal
- Inhalation:exhalation ratio—1:1



For pediatric devices, accurately simulating the physiology of the users may require different breathing patterns, and work is under way to establish appropriate conditions [9].

The recommended procedure for assessing dose uniformity involves a two-stage process. The first step involves capturing the output from the nebulizer on a filter over a specified time, typically 60 seconds, to determine active substance delivery rate. If the delivery rate is low, a longer time may be needed to gather sufficient mass for accurate analysis. In the second part of the test, measurement continues until nebulization stops—i.e., the reservoir empties. Summing the total mass collected in stages one and two determines the total active substance delivered.

Aerodynamic particle size measurement

The regulators recommend cascade impaction for aerodynamic particle size measurement for all inhalation products. A cascade impactor divides a sample into fractions on the basis of particle inertia, a function of aerodynamic particle size. During testing, sample-laden air is drawn through a series of stages each containing a set number of nozzles manufactured to a closely specified diameter [10].

As nozzle diameter decreases, particle/air velocity increases, giving smaller and smaller particles sufficient inertia to break out of the air stream and impact on the collection surface, either a plate or a cup, beneath the stage. Chemical or gravimetric analysis of the amount of drug collected on each surface allows full characterization of the inhaled dose. The analysis also allows further determination of the fine particle dose, the amount of material that, because of its size, will deposit deep in the lungs.

Cascade impaction requires a steady, as opposed to tidal, flow rate, but the testing must, as far as possible, reflect the conditions under which the device operates. EN 13544-1 suggests using a cascade impactor calibrated at 15 L/min or less for testing nebulizers since 15 L/min represents the mid-inhalation flow rate of an adult patient, and the standard mentions the Marple 298X, which was the most suitable impactor at the time. However, because this impactor is calibrated at 2 L/min, the test procedure described by EN 13544-1 samples only 13% of the stream from the nebulizer. Ensuring that this sample represents the entire stream can be challenging, so some labs have used the Andersen Cascade Impactor (ACI) for nebulizer testing, even though the ACI has not been calibrated for this application [11].

Using the NGI for nebulizer testing

In the late 1990s, the consortium that developed and commercialized the NGI aimed to provide the pharmaceutical sector with an impactor closely tailored to its needs. The NGI was originally calibrated for air flows in the range 30 to 100 L/min, but the European Pharmaceutical Aerosol Group (EPAG) initiated a separate calibration carried out at 15 L/min specifically to confirm the suitability of the NGI for nebulizer testing. Rigorous calibration at 15 L/min confirmed the instrument's ability to give sharp cutoff diameters at low flows and, therefore, the NGI's value for nebulizer testing.

At 15 L/min, the seven stages of the NGI produce cutoff diameters in the range of 14.1-0.98 μm , with the last five stages having cutoff diameters between 5.39 and 0.98 μm . These results come close to meeting the original design intent of the NGI to have 5 stages with cutoff diameters less than 5 μm at all working flow rates, even though the flow rate lies outside the defined scope for the project. The study is well documented [12] and provides detailed guidance for NGI operation under these conditions.

At 15 L/min, neither the pre-separator nor the micro orifice collector (MOC) works as intended, so some adjustment to the device is necessary. The pre-sepa-

rator, which becomes dominated by gravitational forces, should therefore be excluded. The MOC, which normally serves as replacement for a paper back-up filter, loses effectiveness at this flow rate because the predicted cutoff diameter increases significantly, making the MOC's collection efficiency similar to that of stage 7. At the 15 L/min flow rate, therefore, the MOC may not effectively collect ultra-fine particles below the stage 7 cutoff. Placing an internal filter below the MOC solves the problem.

The new USP/Ph. Eur. monograph recognizes the suitability of the NGI for nebulizer characterization when used appropriately and recommends it for routine nebulizer testing. In fact, the NGI is the only impactor rigorously calibrated for operation at the 15 L/min recommended for nebulizer testing, which makes it preferable to both the Marple 298X and the ACI. Additionally, the NGI has a larger capacity than the Marple 298X, handles much more easily, and offers a much faster turnaround than the other impactors, with more options for method automation.

Many nebulizer manufacturers recognize that the future of nebulizer testing lies firmly with the NGI, which is already widely used for this application; however, work on method optimization continues. The EPAG nebulizer sub-group is active in this area and is focusing currently on two aspects of routine testing: the need to chill the impactor ahead of measurement and whether or not the NGI collection surfaces should be coated to ensure adequate droplet capture [9].

Pre-measurement impactor cooling

Heat retained in the impactor, even during operation at ambient temperature, can transfer to the droplets, causing evaporation and, consequently, reduction in droplet size during nebulizer testing [12]. If such evaporation occurs, the testing produces an inaccurate particle size distribution biased towards finer droplets. This issue has come sharply into focus since the NGI became the instrument of choice for nebulizer testing because the NGI has a larger thermal mass than either the ACI or Marple 298X.

The new monograph reflects current understanding in this area, recommending assessment of the potential for droplet evaporation during method development. If environmental conditions impact droplet size, the NGI should be cooled before measurement. Several studies have illustrated the effect of cooling the NGI on measured particle size [13,14], and for reasons that remain unclear [15], the magnitude of the observed shift depends on the specific nebulizer tested.

The EPAG nebulization sub-group has embarked on a systematic study of this effect to assess the behav-

ior of three types of device: a conventional non-air entrainment jet nebulizer, an air entrainment jet nebulizer, and a newer vibrating mesh/membrane design. The study will compare the results obtained using an NGI at ambient temperature (20 °C) with those from an NGI pre-cooled to 5 °C.

Preventing evaporative droplet size reduction during testing may be accomplished by placing the NGI in a water bath for the duration of the test or by using a standard refrigerator to pre-cool the instrument to a temperature of between 5 and 10 °C. An alternative approach involves operating with air that is close to saturation, but this method may defeat the accuracy of the test by causing condensational droplet growth. The use of nearly saturated air also fails to provide a method that would be carried out under conditions of normal clinical use.

Assessing the need for cup coating

Cascade impactor testing of all inhaled products routinely involves coating the collection surface, usually with glycerol or silicone oil deposited from a volatile solvent, to reduce particle bounce and re-entrainment. When particles re-entrain in the air flow, they ultimately collect on the wrong surface, distorting the measured particle size. The high jet velocities associated with superior aerodynamic performance make this phenomenon a particular problem for the NGI; however, most experts believe that *liquid* droplets are unlikely to bounce. Work is underway to confirm that cup coating has no effect on particle size measurement, which would allow elimination of that step for nebulizer testing [15].

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