Aerodynamic Particle Size Measurement for Inhalation Liquid Preparations

(吸入液剤の空気力学的粒度測定法)

This test is used to evaluate the fine particle characteristics of the aerosol generated by a nebulizer from inhalation liquid preparations [1, 2].

1. Apparatus

The tests are usually performed using the apparatus 3 in Aerodynamic Particle Size Measurement for Inhalations <*6.15*>, calibrated at a flow rate of 15 L per minute. For the critical dimensions and validation of the apparatus (stage mensuration), also refer to Aerodynamic Particle Size Measurement for Inhalations <*6.15*>. As inhalation liquid preparations should be evaluated at a flow rate lower than the range typically used for dry powder inhalers and metered-dose inhalers, a flow rate of 15 L per minute is recommended. This is based on the typical breathing volume for an adult (500 mL). To quantitatively collect droplets discharged at 15 L per minute, a back-up filter is used in addition to a micro-orifice collector (MOC). The back-up filter is located below the MOC (internal filter option) or using an external filter holder, to collect any fine droplets that pass through the final stage (MOC). A pre-separator is not used to evaluate droplets generated by a nebulizer.

2. Points to consider in the test

2.1 Prevention of evaporation

Controlling the evaporation of droplets produced by a nebulizer is important to avoid bias in the droplet size evaluation process. Evaporation can be minimized by cooling an apparatus to about 5℃, so cool an apparatus in a refrigerator (at about 5℃) for about 90 minutes beforehand[3].

2.2 Over-discharging into the apparatus

In the development and validation of the test method, it should be confirmed that the amount of liquid discharged from a nebulizer is not excessive for the apparatus. If over-discharging does occur, a streaky pattern on the surface of the collection stage can be visually confirmed. This phenomenon is usually associated with an increase in the amount of drug collected at the final stage and the back-up filter. To avoid over-discharging and balance discharged amount and analytical sensitivity, it is most effective to shorten the sampling time (T_0).

2.3 Mass balance (Recovery rate of drugs)

Because of the continuous discharge of drugs from inhalation liquid preparations, it is not easy to evaluate mass balance in the same way as for dry powder inhalers and metered-dose inhalers. Recovery experiments should be conducted as the part of the method development and validation.

2.4 Re-entrainment

Droplets discharged from a nebulizer are less likely to bounce or be re-entrained than solid inhalation particles, so coating the surface of a collection cup is not usually necessary.

2.5 Cleaning of apparatus

The apparatus should usually be thoroughly cleaned, including the inter-stage passageways, at least after each day of use. This is to prevent the corrosion of the metal parts between the stages due to condensation/accumulation of droplets containing salts that occur when the apparatus is cooled. All surfaces of the apparatus should be dried by an appropriate method (e.g., compressed air) after cleaning. However, MOC should not be dried with compressed air.

3. Test procedures

3.1 Preparation

Cool the apparatus and the induction port in a refrigerator (at about 5℃) for more than 90 minutes beforehand. Other methods that can measure while cooling an apparatus at a constant temperature (e.g., use of a cooling cabinet) can be used, if no difference in the results of particle size distribution is validated.

Prepare a nebulizer according to the patient instructions. Fill the nebulizer with a dose of the drug solution according to the dosage and administration of the inhalation liquid preparation to be measured.

Take out the apparatus from the refrigerator. Attach the induction port to the apparatus, and connect the outlet of the apparatus/external filter to a vacuum pump that is capable of drawing air through the apparatus at 15 L per minute, as shown in Fig.1. Connect a flowmeter, calibrated for the volumetric flow leaving the meter, to the induction port. Run the pump, and adjust the flow control valve between the apparatus and the pump to achieve a steady flow of 15 L per minute (±5%). Then, remove the flowmeter from the apparatus.

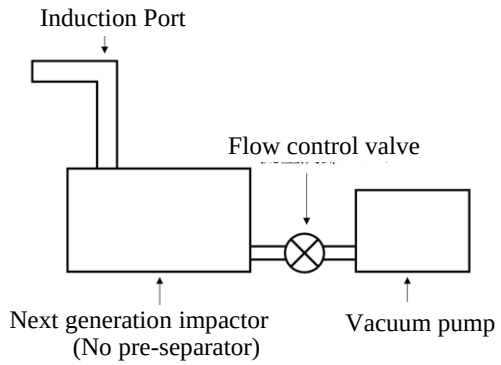

Fig. 1 Configuration of a next generation impactor for the aerodynamic particle size measurement of inhalation liquid preparations

3.2. Measurement

Start measurements within 5 minutes after taking out the apparatus from a refrigerator. Connect the mouthpiece of a nebulizer to the induction port in the same direction as when used by patients. Use a mouthpiece adapter if necessary. Switch on a nebulizer. After collecting drugs for the predefined sampling time (T_0) so that the mass fraction can be calculated, switch off the nebulizer. Remove the nebulizer from the induction port, and switch off the pump. Dismantle the apparatus and determine the amounts of active substance collected in the induction port, all stages, and the back-up filter using a suitable method of analysis, as directed under Aerodynamic Particle Size Measurement for Inhalations <*6.15*>. Drugs collected in the MOC and the back-up filter/external filter are combined and treated as a single sample.

4. Calculation

Calculate the fine particle mass per the specified sampling time (T_0). Calculate the mass fraction ($F_{m,comp}$) of active substance collected at each stage in the apparatus, in order from the induction port, using the following equation:

$$F_{m,comp} = m_{comp} / M$$

m_{comp} = Mass of active substance collected at each stage
M = Total mass of active substance collected from the apparatus

Arrange $F_{m,comp}$ in order of location within the apparatus, beginning at the induction port and ending with the back-up filter (Fig. 2). If multiple stages are reported as a single value due to grouping, the $F_{m,comp}$ values for adjacent stages may be combined.

Calculate the cumulative fraction of active substance of droplets mensurated by the apparatus as directed under Aerodynamic Particle Size Measurement for Inhalations <*6.15*>. Starting at the filter, calculate the cumulative mass of the active substance versus the cut-off diameter of each stage (see Table 1 for the appropriate cut-off diameters of the apparatus 3 at 15 L per minute[4]). Plot the cumulative fraction of the active substance versus the cut-off diameter on an appropriate graph, e.g., a logarithmic graph or a log-probability graph. If necessary, this plot can be used to determine the fraction below a given size or between the upper and lower limits of size by interpolation.

The plot can also be used to determine the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

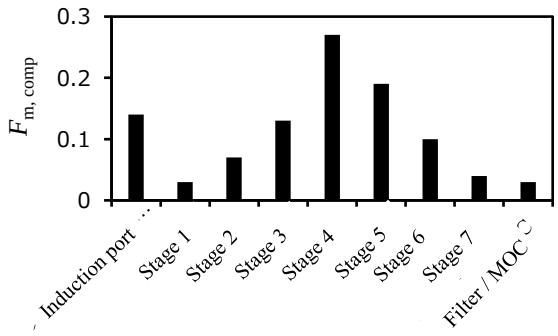

Fig. 2 Example of mass fraction of active substance collected at each stage

Table 1 Cut-off diameters of the apparatus 3 when used at a flow rate of 15 L per minute

Stage	Cut-off diameter (μm)
1	14.1
2	8.61
3	5.39
4	3.30
5	2.08
6	1.36
7	0.98

5. References

1) European Pharmacopoeia 11.0 (2022), 2.9.44. Preparations for Nebulisation: Characterisation.
2) US Pharmacopeia (2023), <1601> Products for Nebulization - Characterization Tests.
3) E. Berg, et al., J. Aerosol Med., 20, 97-104 (2007).
4) V.A. Marple, et al., J. Aerosol Med., 17, 335-343 (2004).