Inhalation Preparations. Page 1092

Change **to**: **Inhalation Preparations**

Inhalation Preparations are liquid or solid preparations intended for administration as vapours or aerosols to the lung in order to obtain a local or systemic effect. They contain one or more active substances that may be dissolved or dispersed in a suitable vehicle.

Inhalation Preparations may, depending on the type of preparation, contain propellants, cosolvents, diluents, antimicrobial preservatives, solubilising and stabilising agents, etc. These excipients do not adversely affect the functions of the mucosa of the respiratory tract or its cilia. Suspensions and emulsions are readily dispersible on shaking and they remain sufficiently stable to enable the correct dose to be delivered. Inhalation Preparations are supplied in single-dose or multidose containers.

Inhalation Preparations intended to be administered as aerosols (dispersions of solid or liquid particles of active ingredient(s) in a gas) are administered by one of the following devices: a nebuliser; an inhaler (pressurised metered-dose inhaler, non-pressurised metered-dose inhaler or powder inhaler).

Several categories of Inhalation Preparations may be distinguished: preparations to be converted into vapour; liquid preparations for nebulisation; pressurised metered-dose preparations for inhalation; non-pressurised metered-dose preparations for inhalation; inhalation powders.

Production

Inhalation preparations should be manufactured in conditions designed to minimise microbial and particulate contamination.

During the development of a preparation that contains an antimicrobial preservative, the effectiveness of the preservative selected, shall be determined as described in 2.2.2. Effectiveness of antimicrobial preservatives.

In the manufacture, packaging, storage and distribution of preparations for inhalation, suitable measures are taken to ensure their microbial quality; recommendations on this aspect are provided in 2.2.9. Microbial contamination in Nonsterile products.

Uniformity of delivered dose of a multidose inhaler must be ensured within a device (intra-inhaler) and between devices (inter-inhaler). For intra-inhaler testing, the uniformity of delivered dose tests are described in the Tests sections of the various preparation categories in this monograph. For inter-inhaler testing, a suitable procedure is to take 10 inhalers and collect a single dose from each inhaler, collecting the dose at the beginning (from 3 inhalers), middle (from 4 inhalers) and end (from 3 inhalers) of the number of doses stated on the label. Other inter-inhaler testing procedures are possible, where justified.

Storage. Avoid storage under extremes of temperature and in an environment with undue fluctuations in temperature.

Labelling. The label states (1) the name(s) of the active ingredient(s); (2) the total amount of the active ingredient(s) in the container except in the case of metered-dose preparation for inhalation); (3) that the container should be shaken before use; (4) the other instructions for use; (5) the date after which the preparation is not intended to be used; (6) the conditions under which it should be stored; (7) a warning that the container is under pressure and that it must not be punctured, broken or incinerated even when apparently empty; (8) the statement.“Warning. Keep away from children”

In the case of metered-dose aerosols and pressurized metered dose inhalers, the label states in addition (1) the total number of deliveries available from the container; (2) the amount of active ingredient(s) released each time the valve is actuated.

In the case of dry powder inhalers the label on the container states (1) the date after which the dry powder inhaler is not intended to be used; (2) the conditions under which the powder for Inhalation should be stored. Where the powder for Inhalation is supplied in a capsule, the label also states;
(3) the quantity of the active ingredient contained in each capsule; (4) that the capsules are intended for use in an inhaler and are not to be swallowed.

Information on use of the preparation provided in the pack shall include (1) the direction for correct use of the aerosol; (2) a warning that the container may explode if punctured, exposed to excessive heat or direct sunlight; (3) the directions for the disposal of the used or partly-used container.

Preparations to be converted into vapour

Preparations intended to be converted into vapour are liquids, solutions, suspensions, emulsions, or semi-solid or solid preparations. They are usually added to hot water and the vapour generated is inhaled.

Liquid preparations for nebulisation

Liquid preparations for nebulisation are solutions, suspensions or emulsions intended to be converted into aerosols by nebulisers.

Liquid preparations for nebulisation in concentrated form are diluted to the prescribed volume with the prescribed liquid before use. Liquid preparations for nebulisation may also be prepared from powders by reconstitution in the prescribed liquid.

The pH of liquid preparations for nebulisation is not lower than 3 and not higher than 10.

Liquid preparations for nebulisation supplied in multi-dose containers may contain a suitable antimicrobial preservative at a suitable concentration except where the preparation itself has adequate antimicrobial properties.

Liquid preparations for nebulisation supplied in multi-dose containers that do not contain an antimicrobial preservative, and where the preparation itself does not have adequate antimicrobial properties, are sterile and are supplied in containers preventing microbial contamination of the contents during storage and use.

Liquid preparations for nebulisation supplied in single-dose containers are sterile and preservative-free, unless otherwise justified and authorised.

Nebulisers are devices that convert liquids into aerosols by high-pressure gases, ultrasonic vibration, and extrusion through a mesh or other methods. They allow the dose to be inhaled at an appropriate active-substance delivery rate over an extended period of time involving consecutive inhalations and with a particle size that allows deposition of the preparation in the lungs.

Nebulisers may be breath-triggered or use other means to synchronise or modify the nebuliser operation with the patient's breathing.

Production

The active substance delivery rate, the total active substance delivered and the particle per droplet-size distribution are determined using the methods described in **Preparations for nebulisation: characterisation.** Where justified and authorised, different apparatus and procedures may be used.

Tests

Prepare the liquid preparation for nebulisation as directed in the instructions to the patient.

Uniformity of content (2.5.4). The test is applicable to Nebulisers that contain less than 10 mg or less than 10 per cent of active ingredient. For Nebulisers containing more than one active ingredient, carry out the test for each active ingredient that corresponds to the above conditions.

The test for uniformity of content should be carried out only after the content of active ingredient(s) in a pooled sample of the nebulisers has been shown to be within accepted limits of stated content.

Uniformity of weight (2.5.3). This test is not applicable to Nebulisers that are required to comply with the test for Uniformity of content for all the active ingredients.

Weigh individually the contents of 20 containers, emptied as completely as possible, and determine the average weight; not more than two of the individual weights deviate from the average weight by more than 10 per cent and none deviate by more than 20 per cent.

Aerodynamic assessment of nebulised aerosols

For liquid preparations for nebulisation that are suspensions, determine fine-particles mass using an apparatus and procedure described in preparations for nebulisation: characterization. Where justified and authorised, a different apparatus and procedure may be used.

Pressurised metered-dose preparations for inhalation

Pressurised metered-dose preparations for inhalation are solutions, suspensions or emulsions supplied in containers equipped with a metering valve and which are held under pressure with (a) suitable propellant(s), which can act also as a solvent.
The delivered dose is the dose delivered from the inhaler. For some preparations the dose has been established as a metered dose. The metered dose is determined by adding the amount deposited on the inhaler to the delivered dose. It may also be determined directly.

Production

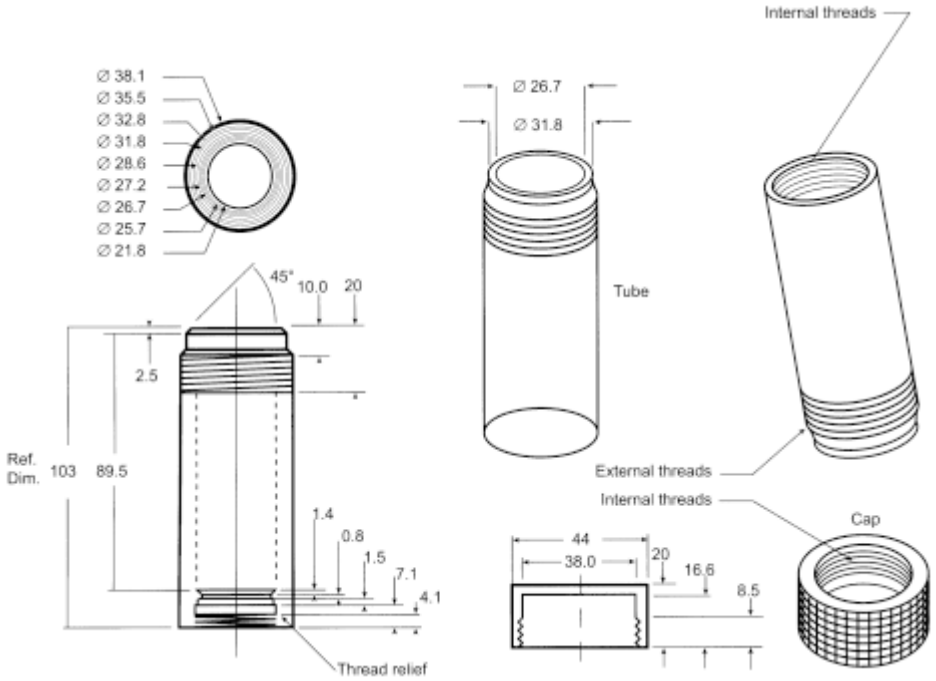
The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of pressurised metered-dose preparations for inhalation are determined using the method described in Preparations for inhalation: aerodynamic assessment of fine particles.

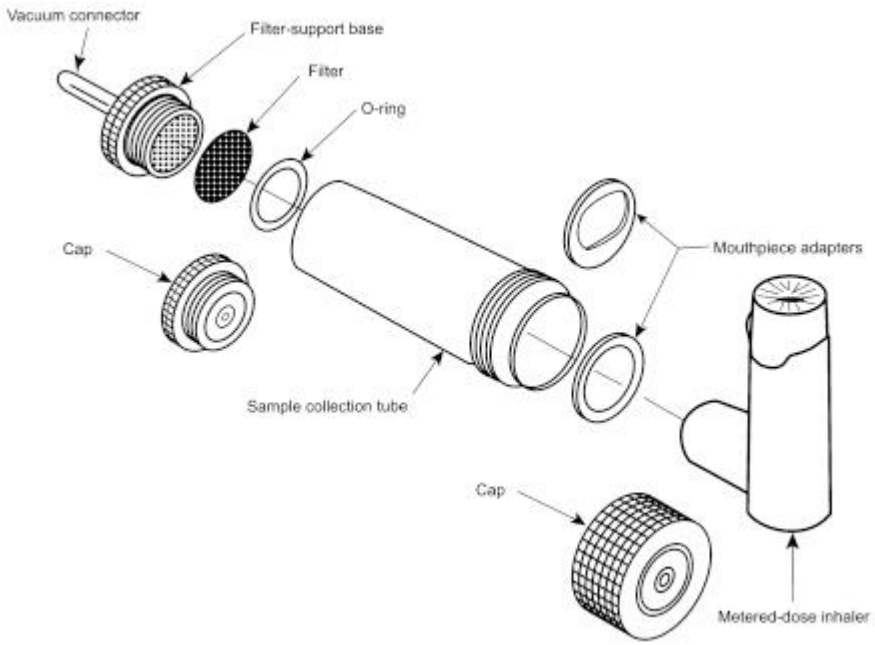
Tests

For breath-triggered pressurised metered-dose inhalers, the test conditions described below may need to be modified to ensure that actuation occurs for the inhaler under test.
Prepare the inhaler as directed in the instructions to the patient.

Uniformity of delivered dose

Pressurised metered-dose inhalers usually operate in a valve-down position. For inhalers that operate in a valve-up position, an equivalent test is applied using methods that ensure the complete collection of the delivered dose.
The dose collection apparatus must be capable of quantitatively capturing the delivered dose.
The following apparatus (Fig. 1) and procedure may be used.





Dimensions in millimeters

Fig. 1: Dose collection apparatus for pressurised metered-dose inhalers

The apparatus consists of a filter-support base with an open-mesh filter-support, such as a stainless steel screen, a collection tube that is clamped or screwed to the filter-support base, and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Use a mouthpiece adapter that ensures that the front face of the inhaler mouthpiece is flush with the front face or the 2.5 mm indented shoulder of the sample collection tube, as appropriate. The vacuum connector is connected to a system comprising a vacuum source and a flow regulator. The source is adjusted to draw air through the complete assembly, including the filter and the inhaler to be tested, at 28.3 litres per minute (± 5 per cent). Air should be drawn continuously through the apparatus to avoid loss of the active substance into the atmosphere. The filter-support base is designed to accommodate 25 mm diameter filter disks. The filter disk and other materials used in the construction of the apparatus must be compatible with the active substance and solvents that are used to extract the active substance from the filter. One end of the collection tube is designed to hold the filter disk tightly against the filter-support base. When assembled, the joints between the components of the apparatus are airtight so that when a vacuum is applied to the base of the filter, all of the air drawn through the collection tube passes through the inhaler.

Unless otherwise prescribed in the instructions to the patient, shake the inhaler for 5 seconds and discharge 1 delivery to waste. Discharge the inverted inhaler into the apparatus, depressing the valve for a sufficient time to ensure complete discharge. Repeat the procedure until the numbers of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance.

Repeat the procedure for a further 2 doses.

Discharge the inhaler to waste, waiting not less than 5 seconds between actuations, until (n/2) + 1 deliveries remain, where n is the number of deliveries stated on the label. Collect 4 doses using the procedure described above.

Discharge the inhaler to waste, waiting not less than 5 seconds between actuations, until 3 doses remain. Collect these 3 doses using the procedure described above.

For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

Unless otherwise justified and authorised, the preparation complies with the test if 9 out of 10 results lie between 75 per cent and 125 per cent of the average value and all lie between 65 per cent and 135 per cent. If 2 or 3 values lie outside the limits of 75 per cent to 125 per cent, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the limits of 75 per cent to 125 per cent and no value lies outside the limits of 65 per cent to 135 per cent.

Fine particle dose

Using an apparatus and procedure described in Preparations for inhalation: aerodynamic assessment of fine particles (apparatus B, C or D), calculate the fine particle dose.

Number of deliveries per inhaler

Take 1 inhaler and discharge the contents to waste, actuating the valve at intervals of not less than 5 seconds. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose).

Leak rate

Take a suitable number of containers, for example 1 container, remove any labels and record the date and time to the nearest half hour. Weigh the container to the nearest milligram and record the mass (M_1) in milligrams. Allow the containers to stand in an upright position at a temperature of 25.0 ± 2.0^o for not less than 3 days, and again weigh the container, recording the mass (M_2) in milligrams, and recording the date and time to the nearest half hour. Determine the time (T), in hours, during which the container was under test.

Calculate the total loss of mass, in milligrams, over the entire shelf life (D), in months, of the container, using the following expression:

$$\frac{730 \text{ X D}}{\text{T}} \text{X } (\text{M}_1 - \text{M}_2)$$

Unless otherwise justified, the preparation complies if the total loss of mass over the entire shelf life is not more than 10 per cent (m/m) of the nominal fill mass of the container.

Non-pressurised metered-dose preparations for inhalation

Non-pressurised metered-dose preparations for inhalation are solutions, suspensions or emulsions for use with inhalers that convert liquids into aerosols using single or multiple liquid jets, ultrasonic vibration or other methods. The volume of liquid to be converted into an aerosol is pre-metered or metered by the inhaler so that the dose delivered from the inhaler can be inhaled with 1 or more inspirations.

Non-pressurised metered-dose preparations for inhalation supplied in multidose containers may contain a suitable antimicrobial preservative at a suitable concentration except where the preparation itself has adequate antimicrobial properties.

Non-pressurised metered-dose preparations for inhalation supplied in multidose containers that do not contain an antimicrobial preservative and where the preparation itself does not have adequate antimicrobial properties, are sterile and are supplied in containers preventing microbial contamination of the contents during storage and use.

Non-pressurised metered-dose preparations for inhalation supplied in single-dose containers are sterile and preservative-free, unless otherwise justified and authorised.

Production

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lung. The fine-particle characteristics of non-pressurised metered-dose preparations for inhalation are determined using the method described in Preparations for inhalation: aerodynamic assessment of fine particles. Alternatively, laser diffraction analysis may be used, when properly validated against method (apparatus B, C or D).

Tests

For breath-triggered non-pressurised metered-dose inhalers, the test conditions described below may need to be modified to ensure that actuation occurs for the inhaler under test.
Prepare the inhaler as directed in the instructions to the patient.

Uniformity of delivered dose

The dose collection apparatus must be capable of quantitatively capturing the delivered dose. The apparatus described in the test for uniformity of delivered dose for pressurised metered-dose preparations may be used.

Discharge the inhaler into the apparatus. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance.

Repeat the procedure for a further 2 doses.

Discharge the inhaler to waste until (n/2) + 1 deliveries remain, where n is the number of deliveries stated on the label. Collect 4 doses using the procedure described above.

Discharge the inhaler to waste until 3 doses remain. Collect these 3 doses using the procedure described above.

For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

Unless otherwise justified and authorised, the preparation complies with the test if 9 out of 10 results lie between 75 per cent and 125 per cent of the average value and all lie between 65 per cent and 135 per cent. If 2 or 3 values lie outside the limits of 75 per cent to 125 per cent, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the limits of 75 per cent to 125 per cent and no value lies outside the limits of 65 per cent to 135 per cent.

Where justified and authorised, another apparatus and procedure may be used.

Fine particle dose

Using an apparatus and procedure described in Preparations for inhalation: aerodynamic assessment of fine particles (apparatus B, C or D), calculate the fine particle dose. Use the same procedure as for pressurised inhalers with appropriate adaptation of the methodology to non-pressurised inhalers. Depending on the characteristics of the non-pressurised metered-dose preparations for inhalation, relative humidity and/or temperature may need to be controlled during the test.

Number of deliveries per inhaler

Take 1 inhaler and discharge the contents to waste. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose).

Inhalation powders

Inhalation powders are supplied in single-dose or multidose containers. To facilitate their use, active substances may be combined with a suitable carrier. They are administered by powder inhalers. For pre-metered inhalers, the inhaler is loaded with powders pre-dispensed in capsules or other suitable dosage forms. For inhalers using a powder reservoir, the dose is created by a metering mechanism within the inhaler.

The delivered dose is the dose delivered from the inhaler. For some preparations, the labelled dose has been established as a metered dose or as a pre-dispensed dose. The metered dose is determined by adding the amount deposited on the inhaler to the delivered dose. It may also be determined directly.

Production

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lung. The fine-particle characteristics of powders for inhalation are determined using the method described in general chapter Preparations for inhalation: aerodynamic assessment of fine particles.

Tests

Prepare the inhaler as directed in the instructions to the patient.

Uniformity of delivered dose

The dose collection apparatus must be capable of quantitatively capturing the delivered dose. A dose collection apparatus similar to that described for the evaluation of pressurised metered-dose inhalers may be used provided that the dimensions of the tube and the filter can accommodate the measured flow rate. A suitable tube is defined in Table 1. Connect the tube to a flow system according to the scheme specified in Fig. 2 and Table 1.

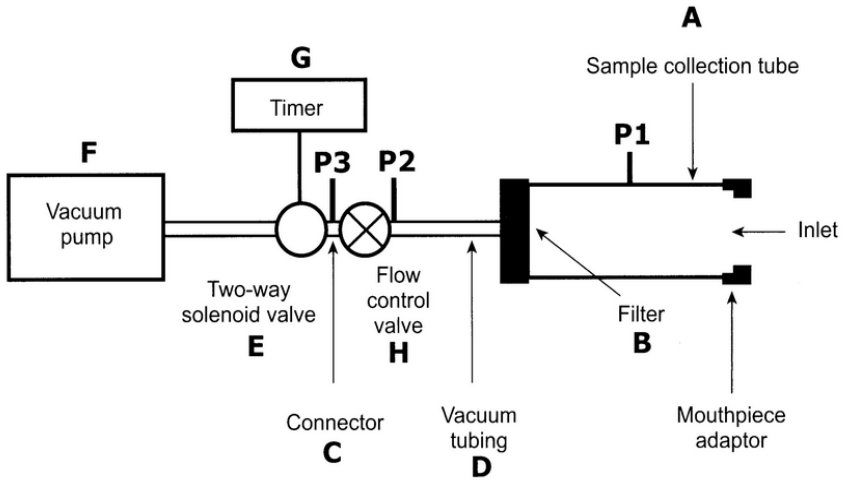


Fig. 2: Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers

Unless otherwise stated, determine the test flow rate and duration using the dose collection tube, the associated flow system, a suitable differential pressure meter and a suitable volumetric flow meter, calibrated for the flow leaving the meter, according to the following procedure.

Table 1: specifications of the apparatus used for powder inhalers described in Fig. 2

Code	Item	Description
A	Sample collection tube	Capable of quantitatively capturing the delivered dose, e.g. dose collection tube similar to that described in Figure A with dimensions of 34.85 mm ID x 12 cm length (e.g. product number XX40 047 00, Millipore Corporation, Bedford, MA 01732 with modified exit tube, ID > 8 mm, fitted with Gelman product number 61631), or equivalent.
B	Filter	47 mm filter, e.g. A/E glass fibre filter (Gelman Sciences, Ann Arbor, MI 48106), or equivalent.
C	Connector	ID > 8 mm, e.g. short metal coupling, with low-diameter branch to P3
D	Vacuum tubing	A length of suitable tubing having an ID > 8 mm and am internal volume of 25 ± 5 ml
E	2-way solenoid valve	A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with

		ID > 8 mm and an opening time < 100 ms (e.g. type 256-A08, Burkert GmbH, D-74653 Ingelfingen), or equivalent.
F	Vacuum pump	Pump must be capable of drawing the required flow rate through the assembled apparatus with the powder inhaler in the mouthpiece adapter (e.g. product type **1** 023, 1423 or 2565, GAST Manufacturing Inc., Benton Harbor, MI 49022), or equivalent. Connect the pump to the 2-way solenoid valve using short and/or wide (> 10 mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
G	Timer	Timer capable of driving the 2-way solenoid valve for the required time period (e.g. type G814, RS Components International, Corby, N N17 9 RS, UK), or equivalent.
PI	Pressure tap	2.2 mm ID, 3.1 mm OD, flush with internal surface of the sample collection tube, centred and burr-free, 59 mm from its inlet. The pressure tap P1 must never be open to the atmosphere.
P2 P3	Pressure measurements	Differential pressure to atmosphere (P1) or absolute pressure (P2 and P3)
H	Flow control valve	Adjustable regulating valve with maximum Cv >1, (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX3 1 1 NP, UK), or equivalent.

Prepare the inhaler for use and connect it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. Use a mouthpiece adapter that ensures that the front face of the inhaler mouthpiece is flush with the front face of the sample collection tube. Connect one port of a differential pressure meter to the pressure reading point P1 in Fig. 2, and let the other be open to the atmosphere. Switch on the pump, open the 2-way solenoid valve and adjust the flow control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H_2O) as indicated by the differential pressure meter. Remove the inhaler from the mouthpiece adapter and, without touching the flow control valve, connect a flowmeter to the inlet of the sampling apparatus. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the following expression:

$$Q_{out} = \frac{Q_{in} \text{ X } P_0}{P_0 - \Delta P}$$

P_0 = Atmospheric pressure,
ΔP = Pressure drop over the meter.

If the flow rate is above 100 liters per minutes adjust the flow control valve to obtain a flow rate of 100 L/min (± 5 per cent). Note the volumetric airflow rate exiting the meter and define this as the test flow rate, Q_{out}, in litres per minute. Define the test flow duration, *T*, in seconds so that a volume of 4 litre of air is drawn from the mouthpiece of the inhaler at the test flow rate, Q_{out}.
Ensure that critical flow occurs in the flow control valve by the following procedure: with the inhaler in place and the test flow rate Q_{out}, measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in Fig. 2); a ratio P3/P2 of less than or equal to 0.5 indicates critical flow; switch to a more powerful pump and re-measure the test flow rate if critical flow is not indicated.

*Pre-metered inhalers***.** Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler using the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance.
Repeat the procedure for a further 9 doses.

Device-metered inhalers. Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler under the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 2 doses.
Discharge the inhaler to waste until (n/2) + 1 deliveries remain, where n is the number of deliveries stated on the label. If necessary, store the inhaler to discharge electrostatic charges. Collect 4 doses using the procedure described above.
Discharge the inhaler to waste until 3 doses remain. If necessary, store the inhaler to discharge electrostatic charges. Collect 3 doses using the procedure described above.
For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

Results. The preparation complies with the test if 9 out of 10 results lie between 75 per cent and 125 per cent of the average value and all lie between 65 per cent and 135 per cent. If 2 or 3 values lie outside the limits of 75 per cent to 125 per cent, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the limits of 75 per cent to 125 per cent and no value lies outside the limits of 65 per cent to 135 per cent.
In justified and authorised cases, these ranges may be extended but no value should be greater than 150 per cent or less than 50 per cent of the mean value. Unless otherwise authorized, the mean value must be between 85 per cent and 115 per cent of the label claim for delivered dose.

Fine particle dose

Using an apparatus and procedure described in Preparations for inhalation: aerodynamic assessment of fine particles (apparatus B, C or D), calculate the fine particle dose.

Number of deliveries per inhaler for multidose inhalers

Discharge doses from the inhaler until empty, at the predetermined flow rate. Record the deliveries discharged. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose).

Preparations for Inhalation: Aerodynamic Assessment of Fine Particles

This test is used to determine the fine particle characteristics of the aerosol clouds generated by preparations for inhalation.

Unless otherwise justified and authorised, one of the following apparatus and test procedures is used.

Stage mensuration. Is performed periodically together with confirmation of other dimensions critical to the effective operation of the impactor.

Re-entrainment (for apparatus B and D). To ensure efficient particle capture, coat each plate with glycerol, silicone oil or similar high viscosity liquid, typically deposited from a volatile solvent. Plate coating must be part of method validation and may be omitted where justified and authorised.

Mass balance. The total mass of the active substance is not less than 75 per cent and not more than 125 per cent of the average delivered dose determined during testing for uniformity of delivered dose. This is not a test of the inhaler but it serves to ensure that the results are valid.

Apparatus A. Glass Impinger

Procedure for nebulisers

Introduce 7 ml and 30 ml of a suitable solvent into the upper and lower impingement chambers, respectively.

Connect all the component parts. Ensure that the assembly is vertical and adequately supported and that the jet spacer peg of the lower jet assembly just touches the bottom of the lower impingement chamber. Connect a suitable pump fitted with a filter (of suitable pore size) to the outlet of the apparatus. Adjust the air flow through the apparatus, as measured at the inlet to the throat, to 60 ± 5 litres per minute.

Introduce the liquid preparation for inhalation into the reservoir of the nebuliser. Fit the mouthpiece and connect it by means of an adapter to the device.

Switch on the pump of the apparatus and after 10 seconds switch on the nebuliser.

After 60 seconds, unless otherwise justified, switch off the nebuliser, wait for about 5 seconds and then switch off the pump of the apparatus. Dismantle the apparatus and wash the inner surface of the upper impingement chamber collecting the washings in a volumetric flask. Wash the inner surface of the lower impingement chamber collecting the washings in a second volumetric flask. Finally, wash the filter preceding the pump and its connections to the lower impingement chamber and combine the washings with those obtained from the lower impingement chamber. Determine the amount of active substance collected in each of the 2 flasks. Express the results for each of the 2 parts of the apparatus as a percentage of the total amount of active substance.

Procedure for pressurised inhalers

Place the actuator adapter in position at the end of the throat so that the mouthpiece end of the actuator, when inserted to a depth of about 10 mm, lines up along the horizontal axis of the throat and the open end of the actuator, which accepts the pressurised container, is uppermost and in the same vertical plane as the rest of the apparatus.

Introduce 7 ml and 30 ml of a suitable solvent into the upper and lower impingement chambers, respectively.

Connect all the component parts. Ensure that the assembly is vertical and adequately supported and that the lower jet-spacer peg of the lower jet assembly just touches the bottom of the lower impingement chamber. Connect a suitable pump to the outlet of the apparatus. Adjust the air flow through the apparatus, as measured at the inlet to the throat, to 60 ± 5 litres per minute.

Prime the metering valve by shaking for 5 seconds and discharging once to waste; after not less than 5 seconds, shake and discharge again to waste. Repeat a further 3 times.

Shake for about 5 seconds, switch on the pump to the apparatus and locate the mouthpiece end of the actuator in the adapter, discharge once immediately. Remove the assembled inhaler from the adapter, shake for not less than 5 seconds, relocate the mouthpiece end of the actuator in the adapter and discharge again. Repeat the discharge sequence. The number of discharges should be minimised and typically would not be greater than 10. After the final discharge wait for not less than 5 seconds and then switch off the pump. Dismantle the apparatus.

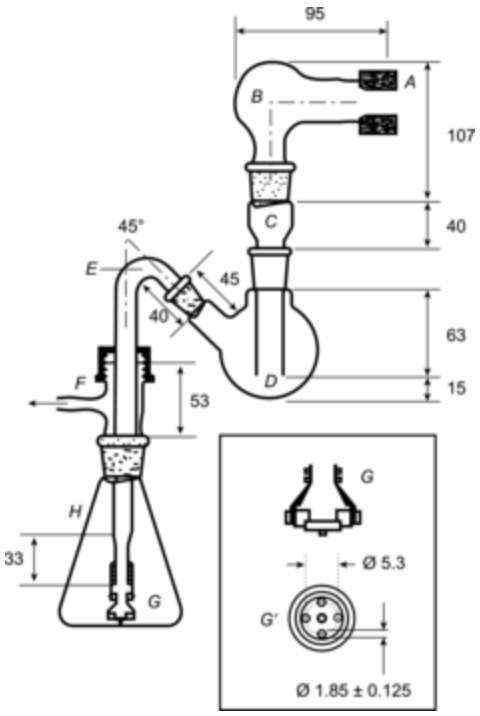
Wash the inner surface of the inlet tube to the lower impingement chamber and its outer surface that projects into the chamber with a suitable solvent, collecting the washings in the lower impingement chamber. Determine the content of active substance in this solution. Calculate the amount of active substance collected in the lower impingement chamber per discharge and express the results as a percentage of the dose stated on the label.

Procedure for powder inhalers

Introduce 7 ml and 30 ml of a suitable solvent into the upper and lower impingement chambers, respectively.
Connect all the component parts. Ensure that the assembly is vertical and adequately supported and that the jet-spacer peg of the lower jet assembly just touches the bottom of the lower impingement chamber. Without the inhaler

in place, connect a suitable pump to the outlet of the apparatus. Adjust the air flow through the apparatus, as measured at the inlet to the throat, to 60 ± 5 litres per minute.

Prepare the inhaler for use and locate the mouthpiece in the apparatus by means of a suitable adapter. Switch on the pump for 5 seconds. Switch off the pump and remove the inhaler. Repeat the discharge sequence. The number of discharges should be minimised and typically would not be greater than 10. Dismantle the apparatus.
Wash the inner surface of the inlet tube to the lower impingement chamber and its outer surface that projects into the chamber with a suitable solvent, collecting the washings in the lower impingement chamber. Determine the content of active substance in this solution. Calculate the amount of active substance collected in the lower impingement chamber per discharge and express the results as a percentage of the dose stated on the label.



Dimensions in millimetres (tolerances ± 1 mm unless otherwise prescribed)

Fig. 3: Apparatus A: glass impinger

Table 2. – Component specification for apparatus A in Figure 3

Code	Item	Description	Dimensions*
A	Mouthpiece adaptor	Moulded rubber adapter for actuator mouthpiece.	
B	Throat	Modified round-bottomed flask:	50 ml
		ground-glass inlet socket	29/32
		ground-glass outlet cone	24/29
C	Neck	Modified glass adapter:	
		ground-glass inlet socket	24/29
		ground-glass outlet cone	24/29
		Lower outlet section of precision-bore glass tubing:	
		bore diameter	14
		Selected bore light-wall glass tubing:	
		external diameter	17
D	Upper impingement chamber	Modified round-bottomed flask	100 ml
		ground-glass inlet socket	24/29

		ground-glass outlet cone	24/29
E	Coupling tube	Medium-wall glass tubing:	
		ground-glass cone	14/23
		Bent section and upper vertical section:	
		external diameter	13
		Lower vertical section:	
		external diameter	8
F	Screw thread, side-arm adaptor	Plastic screw cap	28/13
		Silicone rubber ring	28/11
		PTFE washer	28/11
		Glass screw thread:	
		thread size	28
		Side-arm outlet to vacuum pump:	
		minimum bore diameter	5
G	Lower jet assembly	Modified polypropylene filter holder connected to lower vertical section of coupling tube by PTFE tubing.	see Fig. 3
		Acetal circular disc with the centres of four jets arranged on a projected circle of diameter 5.3 mm with an integral jet spacer peg:	10
		peg diameter	2
		peg protrusion	2
H	Lower impingement chamber	Conical flask	250 ml
		ground-glass inlet socket	24/29

Apparatus B. Andersen Cascade impactor.

The Andersen 1 ACFM non-viable cascade impactor consists of 8 stages together with a final filter. Material of construction may be aluminium, stainless steel or other suitable material. The stages are clamped together and sealed with O-rings. Critical dimensions applied by the manufacturer of apparatus B are provided in Table 3. In use, some occlusion and wear of holes will occur. In-use mensuration tolerances need to be justified. In the configuration used for pressurised inhalers (Fig. 4) the entry cone of the impactor is connected to an induction port (Fig. 9). A suitable mouthpiece adapter is used to provide an airtight seal between the inhaler and the induction port. The front face of the inhaler mouthpiece must be flush with the front face of the induction port.

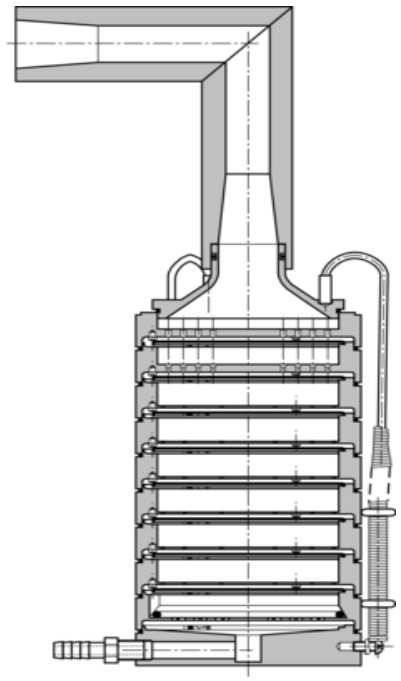
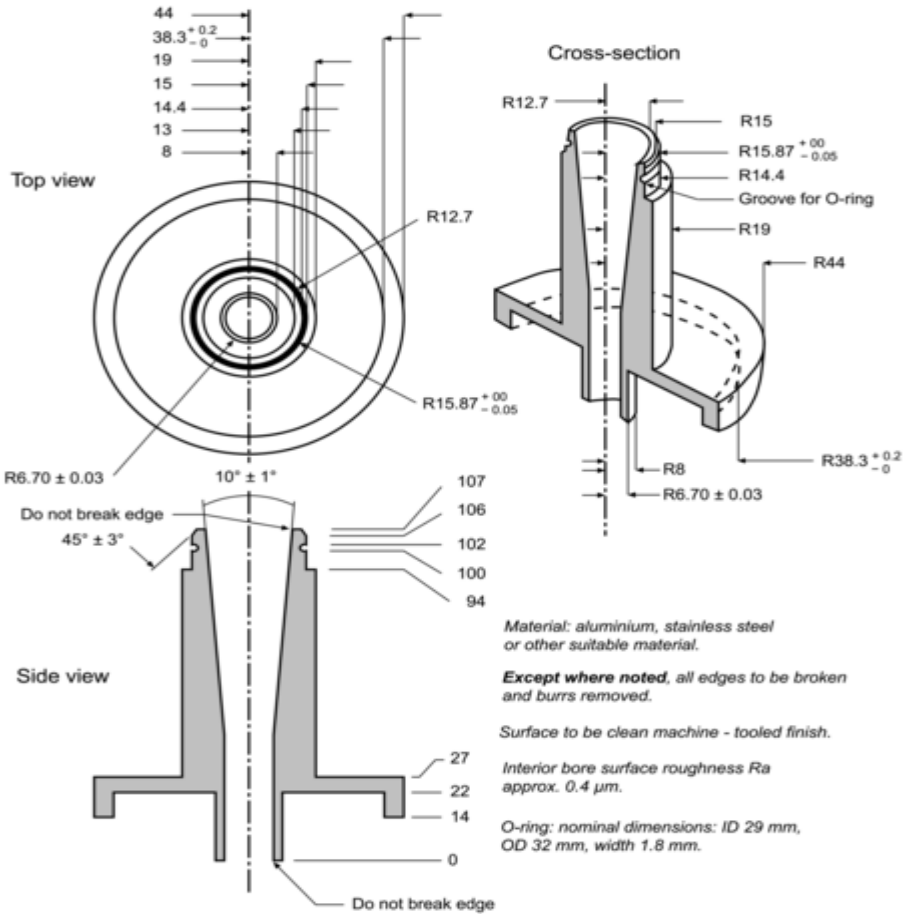


Fig. 4: Apparatus B. Andersen cascade impactor used for pressurised inhalers

In the configuration for powder inhalers, a pre-separator is placed above the top stage to collect large masses of non-respirable powder. It is connected to the induction port as shown in Fig. 5. To accommodate high flow rates through the impactor, the outlet nipple, used to connect the impactor to the vacuum system is enlarged to have an internal diameter of greater than or equal to 8 mm.

Table 3 – Critical dimensions for apparatus B

Description	**Number**	**Dimension (mm)**
Stage 0 nozzle diameter	96	2.55 ± 0.025
Stage 1 nozzle diameter	96	1.89 ± 0.025
Stage 2 nozzle diameter	400	0.914 ± 0.0127
Stage 3 nozzle diameter	400	0.711 ± 0.0127
Stage 4 nozzle diameter	400	0.533 ± 0.0127
Stage 5 nozzle diameter	400	0.343 ± 0.0127
Stage 6 nozzle diameter	400	0.254 ± 0.0127
Stage 7 nozzle diameter	201	0.254 ± 0.0127



(Dimensions in millimetres unless otherwise stated)

Fig. 5: Connection of the induction port to the preseparator of the Andersen cascade impactor

Procedure for pressurised inhalers

Assemble the Andersen impactor with a suitable filter in place. Ensure that the system is airtight. In that respect, follow the manufacturer's instructions. Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the actuator, when inserted, lines up along the horizontal axis of the induction port and the inhaler unit is positioned in the same orientation as the intended use. Connect a suitable pump to the outlet of the apparatus and adjust the air flow through the apparatus, as measured at the inlet to the induction port, to 28.3 litres per minute (± 5 per cent). Switch off the pump.

Unless otherwise prescribed in the patient instructions shake the inhaler for 5 seconds and discharge one delivery to waste. Switch on the pump to the apparatus, locate the mouthpiece end of the actuator in the adapter and discharge the inverted inhaler into the apparatus, depressing the valve for a sufficient time to ensure complete discharge. Wait for 5 seconds before removing the assembled inhaler from the adapter. Repeat the procedure. The number of discharges should be minimised and typically would not be greater than 10. The number of discharges is sufficient to ensure an accurate and precise determination of the fine particle dose. After the final discharge, wait for 5 seconds and then switch off the pump.

Dismantle the apparatus. Carefully remove the filter and extract the active substance into an aliquot of the solvent. Remove the induction port and mouthpiece adapter from the apparatus and extract the active substance into an aliquot of the solvent. Extract the active substance from the inner walls and the collection plate of each of the stages of the apparatus into aliquots of solvent.

Using a suitable method of analysis, determine the quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (see Calculations).

Procedure for powder inhalers

The aerodynamic cut-off diameters of the individual stages of this apparatus are currently not well-established at flow rates other than 28.3 litres per minute.
Users must justify and validate the use of the impactor in the chosen conditions, when flow rates different from 28.3 litres per minute are selected.

Assemble the Andersen impactor with the pre-separator and a suitable filter in place and ensure that the system is airtight. Depending on the product characteristics, the pre-separator may be omitted, where justified and authorised. Stages 6 and 7 may also be omitted at high flow rates, if justified. The pre-separator may be coated in the same way as the plates or may contain 10 ml of a suitable solvent. Connect the apparatus to a flow system according to the scheme specified in Fig. 10 and Table 6.

Unless otherwise defined, conduct the test at the flow rate, Q_{out}, used in the test for uniformity of delivered dose drawing 4 litres of air from the mouthpiece of the inhaler and through the apparatus.
Connect a flow meter to the induction port. Use a flow meter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the following expression:

$$Q_{out} = \frac{Q_{in} \text{ X } P_0}{P_0 - \Delta P}$$

P_0 = Atmospheric pressure,
ΔP = Pressure drop over the meter.

Adjust the flow control valve to achieve steady flow through the system at the required rate, Q_{out} (± 5 per cent). Ensure that critical flow occurs in the flow control valve by the procedure described for Apparatus C. Switch off the pump.

Prepare the powder inhaler for use according to the patient instructions. With the pump running and the 2-way solenoid valve closed, locate the mouthpiece of the inhaler in the mouthpiece adapter. Discharge the powder into the apparatus by opening the valve for the required time, T (± 5 per cent). Repeat the discharge sequence. The number of discharges should be minimised and typically would not be greater than 10. The number of discharges is sufficient to ensure an accurate and precise determination of fine particle dose.

Dismantle the apparatus. Carefully remove the filter and extract the active substance into an aliquot of the solvent. Remove the pre-separator, induction port and mouthpiece adapter from the apparatus and extract the active substance into an aliquot of the solvent. Extract the active substance from the inner walls and the collection plate of each of the stages of the apparatus into aliquots of solvent.

Using a suitable method of analysis, determine the quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (see Calculations).

Apparatus C. Multi-stage liquid impinger

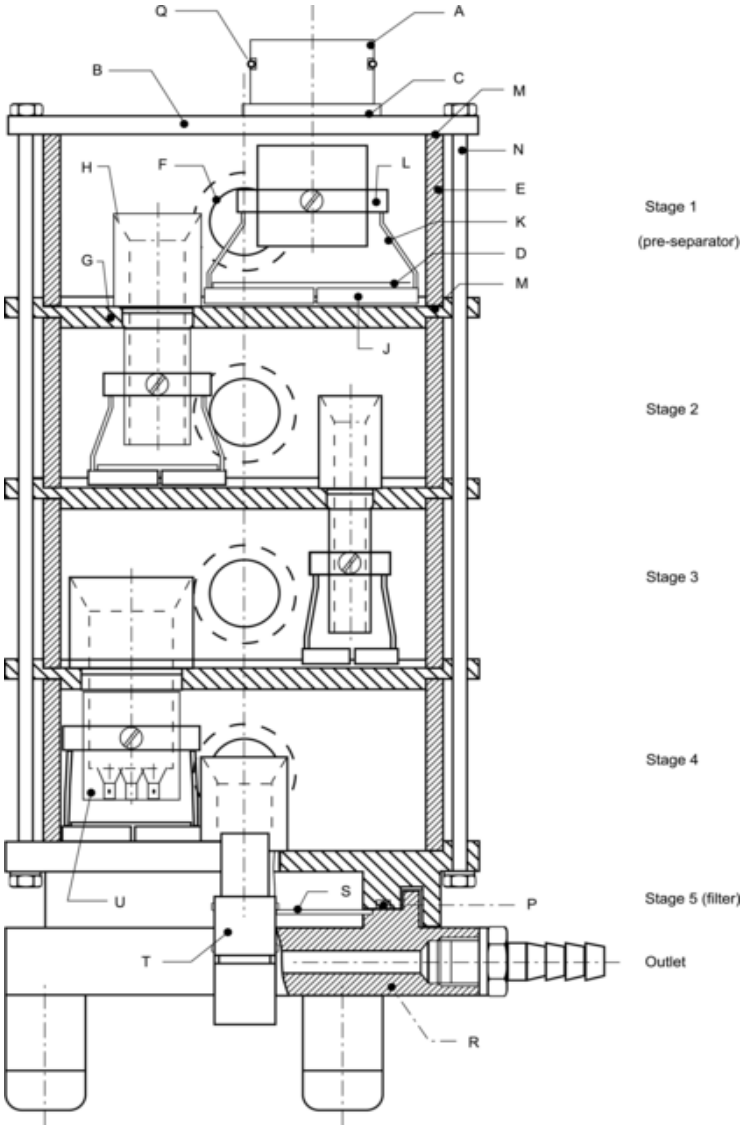


Fig. 6: Multi-stage liquid impinger

The multi-stage liquid impinger consists of impaction stages 1 (Pre-separator), 2, 3 and 4 and an integral filter stage (stage 5) (see Fig. 6/8). An impaction stage comprises an upper horizontal metal partition wall (B) through which a metal inlet jet lube (A) with its impaction plate (D) is protruding. A glass cylinder (E) with sampling port (F) forms the vertical wall of the stage, and a lower horizontal metal partition wall (G) through which the tube (H) connects to the next lower stage. The tube into stage 4 (U) ends in a multi-jet arrangement. The impaction plate (D) is secured in a metal frame (J) which is fastened by 2 wires (K) to a sleeve (L) secured on the jet tube. The horizontal face of the collection plate is perpendicular to the axis of the jet tube and centrally aligned. The upper surface of the impaction plate is slightly raised above the edge of the metal frame. A recess around the perimeter of the horizontal partition wall guides the position of the glass cylinder. The glass cylinders are sealed against the horizontal partition walls with gaskets (M) and clamped together by 6 bolts (N). The sampling ports are sealed by stoppers. The bottom-side of the lower partition wall of Stage 4 has a concentrical protrusion fitted with a rubber O-ring (P) which seals against the edge of a filter placed in the filter holder. The filter holder (R) is constructed as a basin with a concentrical recess in which a perforated filter support (S) is flush-fitted. The filter holder is dimensioned for 76 mm diameter filters. The assembly of impaction stages is clamped onto the filter holder by 2 snap-locks (T). Connect an induction port (see Fig. 9) onto the stage 1 inlet jet tube of the impinger. A rubber O-ring on the jet tube provides an airtight connection to the induction port. A suitable mouthpiece adapter is used to provide an airtight seal between

the inhaler and the induction port. The front face of the inhaler mouthpiece must be flush with the front face of the induction port.

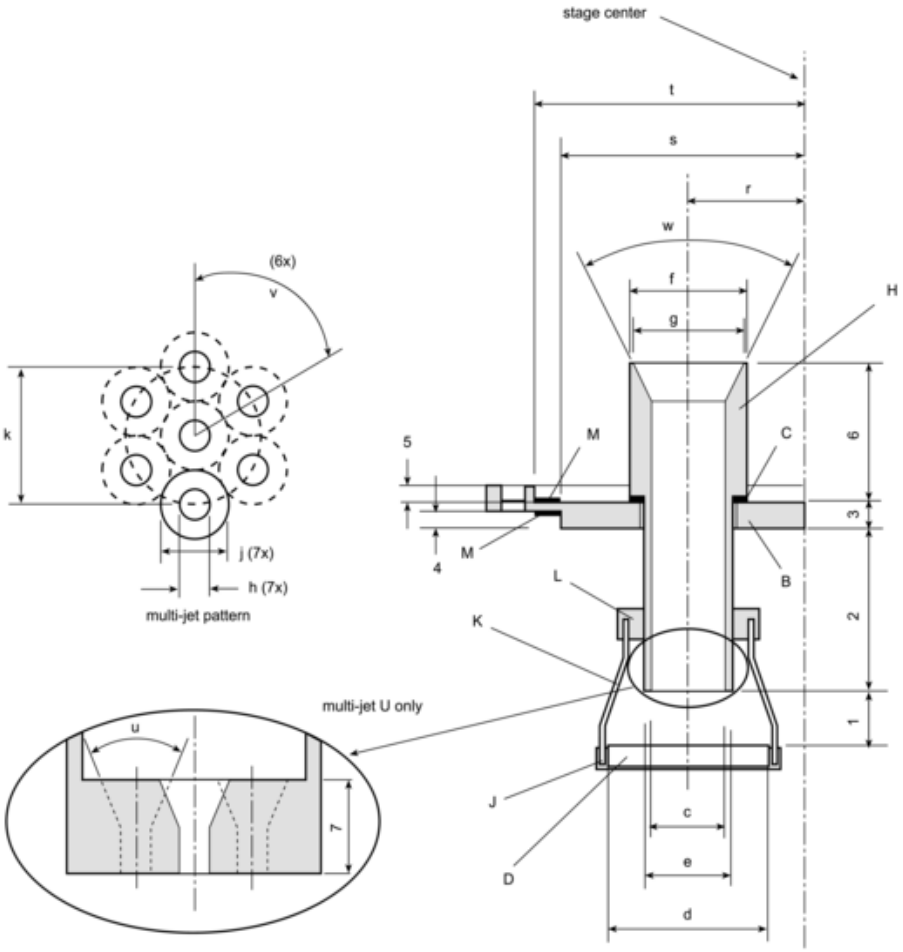


Fig. 7: Details of jet tube and impaction plate. Inserts show end of multi-jet tube U leading to stage 4. (Numbers and lowercase letters refer to Table 5 and uppercase letters refer to Fig. 6.

Procedure for pressurised inhalers

Dispense 20 ml of a solvent, capable of dissolving the active substance into each of stages 1 to 4 and replace the stoppers. Tilt the apparatus to wet the stoppers, thereby neutralising electrostatic charge. Place a suitable filter capable of quantitatively collecting the active substance in stage 5 and assemble the apparatus. Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the actuator, when inserted, lines up along the horizontal axis of the induction port and the inhaler is positioned in the same orientation as intended for use. Connect a suitable vacuum pump to the outlet of the apparatus and adjust the air flow through the apparatus, as measured at the inlet to the induction port, to 30 litres per minute (± 5 per cent). Switch off the pump.

Unless otherwise prescribed in the patient instructions shake the inhaler for 5 seconds and discharge 1 delivery to waste. Switch on the pump to the apparatus, locate the mouthpiece end of the actuator in the adapter and discharge the inhaler into the apparatus, depressing the valve for a sufficient time to ensure complete discharge. Wait for 5 seconds before removing the assembled inhaler from the adapter. Repeat the procedure. The number of discharges should be minimised and typically would not be greater than 10. The number of discharges is sufficient to ensure an

accurate and precise determination of the fine particle dose. After the final discharge, wait for 5 seconds and then switch off the pump.

Dismantle the filter stage of the apparatus. Carefully remove the filter and extract the active substance into an aliquot of the solvent. Remove the induction port and mouthpiece adapter from the apparatus and extract the active substance into an aliquot of the solvent. If necessary, rinse the inside of the inlet jet tube 10 stage 1 with solvent, allowing the solvent to flow into the stage. Extract the active substance from the inner walls and the collection plate of each of the 4 upper stages of the apparatus into the solution in the respective stage by carefully tilting and rotating the apparatus, observing that no liquid transfer occurs between the stages.

Using a suitable method of analysis, determine the quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (sec Calculations).

Table 4 – Components specification in for apparatus C in Fig. 6/8

Code	**Item**	**Description**	**Dimensions****
A,H	Jet tube	Metal tube screwed onto partition wall sealed by gasket (C), polished inner surface	See Fig. 7
B,G	Partition Wall	Circular metal plate	
		– Diameter	120
		– thickness	See Fig. 7
C	Gasket	e.g. PTFE	to fit jet tube
D	Impaction Plate	Porosity 0 sintered-glass disk	See Fig. 7
E	Glass Cylinder	Plane polished cut glass tube	
		– height, including gaskets	46
		– outer diameter	100
		– wall thickness	3.5
		– sampling port (F) diameter	18
		– stopper in sampling port	ISO 24/25
J	Metal frame	L-profiled circular frame with slit	
		– inner diameter	to fit impaction plate
		– height	4
		– thickness of horizontal section	0.5
		– thickness of vertical section	2
K	Wire	Steel wire interconnecting metal frame and sleeve (2 for each frame)	
		– diameter	1
L	Sleeve	Metal sleeve secured on jet tube by screw	
		– inner diameter	to fit jet tube
		– height	6
		– thickness	5
M	Gasket	e.g. silicone	to fit glass cylinder
N	Bolt	Metal bolt with nut (6 pairs)	

		– length	205
		– diameter	4
P	O-ring	Rubber O-ring	
		– diameter x thickness	66.34 x 2.62
Q	O-ring	Rubber O-ring	
		– diameter x thickness	29.1 x 1.6
R	Filter holder	Metal housing with stand and outlet	See Fig. 8
S	Filter support	Perforated sheet metal	
		– diameter	66
		– hole diameter	3
		– distance between holes (centre-points)	4
T	Snap-locks		
U	Multi-jet tube	Jet tube (H) ending in multi-jet arrangement.	See inserts Fig. 7

* Refers to Fig. 6.

** Measures in millimeters with tolerances according to iso 2768-m unless otherwise stated.

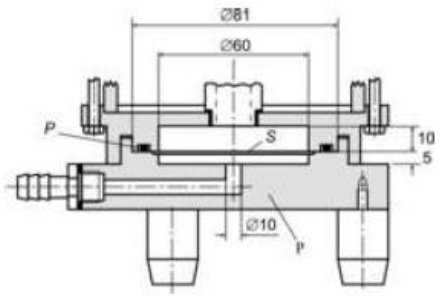


Fig. 8: Details of the filter stage (stage 5). Numbers refer to dimensions (≥ Ø = diameter). Uppercase letters refer to Table 4.

Dimensions in millimetres unless otherwise stated

Table 5 – Dimensions[(1)] of jet tube with impaction plate

Type	Code [(2)]	Stage 1	Stage 2	Stage 3	Stage 4	Filter (stage 5)
Distance	1	9.5 (-.0+.5)	5.5 (-.0+.5)	4.0 (-.0+.5)	6.0 (-.0+.5)	n.a
Distance	2	26	31	33	30.5	0
Distance	3	8	5	5	5	5
Distance	4	3	3	3	3	n.a
Distance	5	0	3	3	3	3
Distance	6[(3)]	20	25	25	25	25
Distance	7	n.a	n.a	n.a	8.5	n.a
Diameter	c	25	14	8.0 (± .1)	21	14
Diameter	d	50	30	20	30	n.a

Diameter	e	27.9	16.5	10.5	23.9	n.a
Diameter	f	31.75 (.0+.5)	22	14	31	22
Diameter	g	25.4	21	13	30	21
Diameter	h	n.a	n.a	n.a	2.70 (± .5)	n.a
Diameter	j	n.a	n.a	n.a	6.3	n.a
Diameter	k	n.a	n.a	n.a	12.6	n.a
Radius	r	16	22	27	28.5	0
Radius	s	46	46	46	46	n.a
Radius	t	n.a	50	50	50	50
Angle	w	10^0	53^0	53^0	53^0	53^0
Angle	u	n.a	n.a	n.a	45^0	n.a

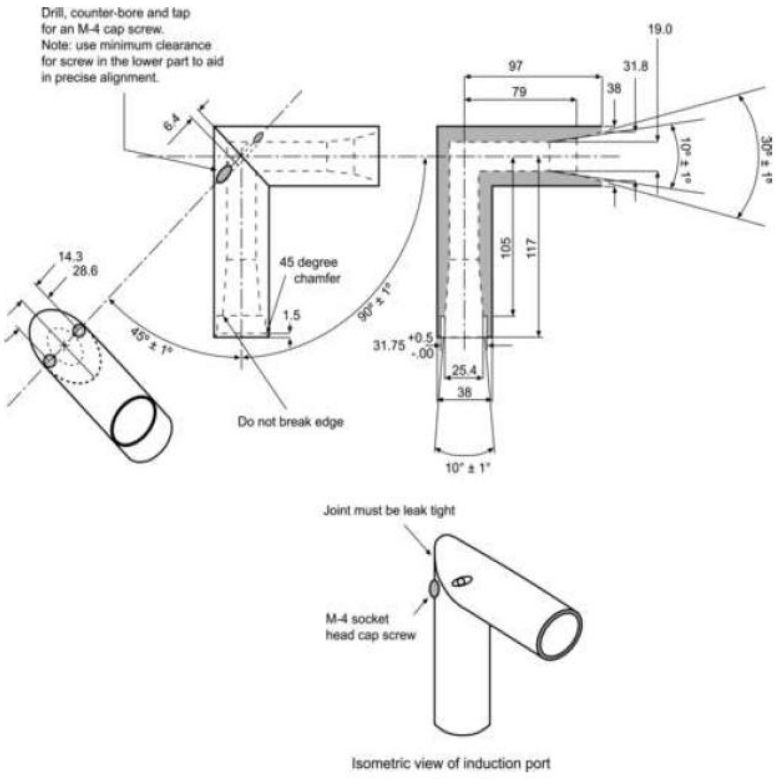
(1) Measures in millimeters with tolerances according to ISO 2768-m unless otherwise stated

(2) Refer to Fig. 7

(3) Including gasket

(4) Relative centreline of stage compartment

n.a. = not applicable



Note:

1. Material may be aluminium, stainless steel or other suitable material.
2. Machine from 38 mm bar stock.
3. Bore 19 mm hole through bar.
4. Cut tube to exact 45^0 as shown.

5. The inner bores and tapers should be smooth - surface roughness Ra approx. 0.4µm.
6. Mill joining cads of stock to provide a liquid tight leak-free seal.
7. Set up a holding fixture for aligning the inner 19 mm bore and for drilling and tapping M4 X 0.7 threads. There must be virtually no mismatch of the inner bores in the miter joint.

Dimensions in millimetres unless otherwise stated

Fig. 9: Induction Port

Procedure for powder inhalers

Place a suitable low resistance filter capable of quantitatively collecting the active substance in stage 5 and assemble the apparatus. Connect the apparatus to a flow system according to the scheme specified in Fig. 10 and Table 6. Unless otherwise defined, conduct the test at the flow rate, Q_{out}, used in the test for uniformity of delivered dose, drawing 4 litre of air from the mouthpiece of the inhaler and through the apparatus.
Connect a flow meter to the induction port. Use a flow meter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow *(*Q_{in}*)*, use the following expression:

$$Q_{out} = \frac{Q_{in} \text{ X } P_0}{P_0 - \Delta P}$$

Po = atmospheric pressure,
ΔP = pressure drop over the meter.

Adjust the flow control valve to achieve steady flow through the system at the required rate, Q_{out} (± 5 per cent). Switch off the pump. Ensure that critical flow occurs in the flow control valve by the following procedure.

With the inhaler in place and the test flow rate established, measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in Fig. 10). A ratio P3/P2 of less than or equal to 0.5 indicates critical flow. Switch to a more powerful pump and re-measure the test flow rate if critical flow is not indicated.
Dispense 20 ml of a solvent, capable of dissolving the active substance into each of the 4 upper stages of the apparatus and replace the Stoppers. Tilt the apparatus to wet the stoppers, thereby neutralising electrostatic charge. Place a suitable mouthpiece adapter in position at the end of the induction port.

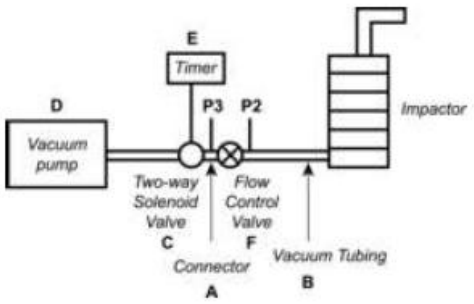


Fig. 10: Experimental set-up for testing powder inhalers

Table 6 – Component specification for Fig. 10

Code	Item	Description
A	Connector	ID ≥ 8 mm, e.g., short metal coupling, with low-diameter branch to P3
B	Vacuum tubing	A length of suitable tubing having an ID ≥ 8 mm and an internal volume of

		25 ± 5 ml.
C	2-way solenoid valve	A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with ID ≥ 8 mm and an opening time ≤ 100 ms. (e.g. type 256-A08, Burkert GmbH, D-74653 Ingelfingen), or equivalent.
D	Vacuum pump	Pump must be capable of drawing the required flow rate through the assembled apparatus with the powder inhaler in the mouthpiece adapter (e.g. product type 1023, 1423 or 2565, Gast Manufacturing Inc., Benton Harbor, MI 49022), or equivalent. Connect the pump to the 2-way solenoid valve using short and/or wide (ID ≥ 10 mm) vacuum tubing and connectors to minimize pump capacity requirements.
E	Timer	Timer capable to drive the 2-way solenoid valve for the required duration (e.g. type G814, RS Components International, Corby, NN17 9RS, UK), or equivalent.
P2 P3	Pressure measurements	Determine under steady-state flow condition with an absolute pressure transducer.
F	Flow control valve	Adjustable regulating valve with maximum $C_V \geq 1$, (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent.

Prepare the powder inhaler for use according to patient instructions. With the pump running and the 2-way solenoid valve closed, locate the mouthpiece of the inhaler in the mouthpiece adapter. Discharge the powder into the apparatus by opening the valve for the required time, T (± 5 per cent). Repeat the procedure. The number of discharges should be minimised and typically would not greater than 10. The number of discharges is sufficient to ensure an accurate and precise determination of fine particle dose.

Dismantle the filter stage of the apparatus. Carefully remove the filter and extract the active substance into an aliquot of the solvent. Remove the induction port and mouthpiece adapter from the apparatus and extract the active substance into an aliquot of the solvent. If necessary, rinse the inside of the inlet jet tube to stage 1 with solvent, allowing the solvent to flow into the stage. Extract the active substance from the inner walls and the collection plate of each of the 4 upper stages of the apparatus into the solution in the respective stage by carefully tilting and rotating the apparatus, observing that no liquid transfer occurs between the stages.

Using a suitable method of analysis, determine the amount of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (see Calculations).

Apparatus D. Cascade impactor with 7 Stages and a Micro orifice collector (MOC)

Appararus D is a cascade impactor with 7 stages and a micro-orifice collector (MOC). Over the flow fate range of 30 liter per minutes to 100 litres per minutes the 50 per cent efficiency cut-off diameters (D_{50} values) range between 0.24 µm to 11.7 µm, evenly spaced on a logarithmic scale. In this flow range, there are always at least 5 stages with D_{50} values between 0.5 µm and 6.5 µm. The collection efficiency curves for each stage are sharp and minimise overlap between stages.

Material of construction may be aluminium, stainless steel or other suitable material.

The impactor configuration has removable impaction cups with all the cups in one plane (Fig. 11/14). There are 3 main sections to the impactor; the bottom frame that holds the impaction cups, the seal body that holds the jets and the lid that contains the interstage passageways (Fig. 11/12). Multiple nozzles are used at all but the first stage (Fig. 13). The flow passes through the impactor in a saw-tooth pattern.

Critical dimensions are provided in Table 7.

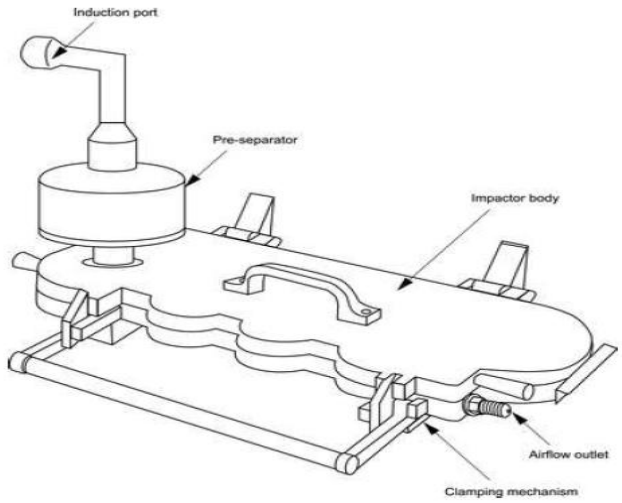


Fig. 11: Apparatus D (Shown with the pre-separator in place)

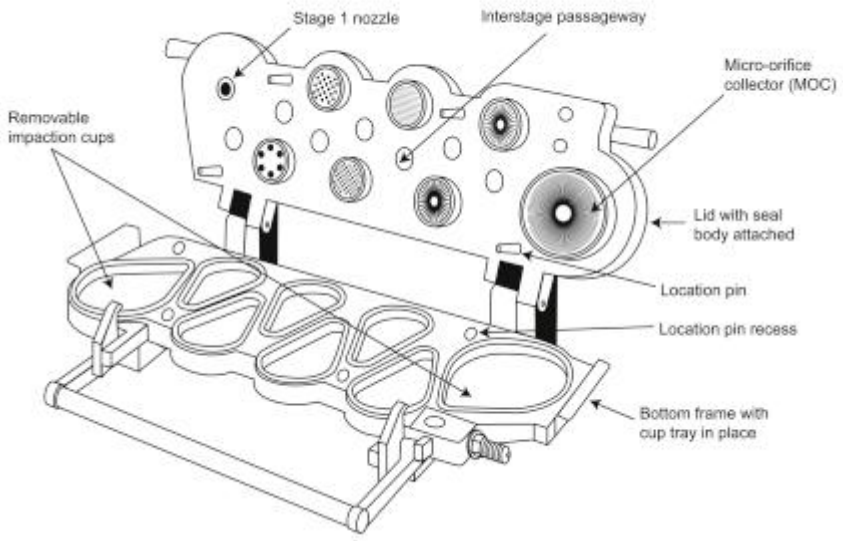


Fig. 12: Apparatus D showing component parts

Table 7– Critical dimensions for apparatus D

Description	**Dimension (mm)**
Pre-separator (dimension a - see Fig. 15)	12.8 ± 0.005
Stage 1* Nozzle diameter	14.3 ± 0.005
Stage 2* Nozzle diameter	4.88 ± 0.004

Stage 3* Nozzle diameter	2.185 ± 0.002
Stage 4* Nozzle diameter	1.207 ± 0.001
Stage 5* Nozzle diameter	0.608 ± 0.001
Stage 6* Nozzle diameter	0.323 ± 0.001
Stage 7* Nozzle diameter	0.206 ± 0.001
MOC*	Approx. 0.070
Cup depth (dimension b- see Fig. 14)	14.625 ± 0.10
Collection cup surface roughness (Ra)	0.5 – 2 µm
Stage 1 nozzle to seal body distance** - dimension C	0 ± 1.18
Stage 2 nozzle to seal body distance** - dimension C	5.236 ± 0.736
Stage 3 nozzle to seal body distance** - dimension C	8.445 ± 0.410
Stage 4 nozzle to seal body distance** - dimension C	11.379 ± 0.273
Stage 5 nozzle to seal body distance** - dimension C	13.176 ± 0.341
Stage 6 nozzle to seal body distance** - dimension C	13.999 ± 0.071
Stage 7 nozzle to seal body distance** - dimension C	14.000 ± 0.071
MOC nozzle to seal body distance** - dimension C	14.429 to 14.571

* see Fig. 13

** see Fig. 14

In routine operation, the seal body and lid are held together as a single assembly. The impaction cups are accessible when this assembly is opened at the end of an inhaler test. The cups are held in a support tray, so that all cups can be removed from the impactor simultaneously by lifting out the tray.

An induction port with internal dimensions (relevant to the airflow path) defined in Fig. 9 connects to the impactor inlet. A pre-separator can be added when required, typically with powder inhalers, and connects between the induction port and the impactor. A suitable mouthpiece adapter is used to provide an airtight seal between the inhaler and the induction port.

Apparatus D contains a terminal Micro-Orifice Collector (MOC) that for most formulations will eliminate the need for a final filter as determined by method validation. The MOC is an impactor plate with nominally 4032 holes, each approximately 70 µm in diameter. Most particles not captured on stage 7 of the impactor will be captured on the cup surface below the MOC. For impactors operated at 60 liter per minutes, the MOC is capable of collecting 80 per cent of 0.14 µm particles. For formulations with a significant fraction of particles not captured by the MOC, there is an optional filter holder that can replace the MOC or be placed downstream of the MOC (a glass fibre filter is suitable).

Procedure for pressurised inhalers

Place cups into the apertures in the cup tray. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with the seal body attached and operate the handle to lock the impactor together so that the system is airtight.

Connect an induction port with internal dimensions defined in Fig. 9 to the impactor inlet. Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the actuator, when inserted, lines up along the horizontal axis of the induction port. The front face of the inhaler mouthpiece must be flush with the front face of the induction port. When attached to the mouthpiece adapter, the inhaler is positioned in the same orientation as intended for use. Connect a suitable pump to the outlet of the apparatus and adjust the air

flow through the apparatus, as measured at the inlet to the induction port, to 30 liter per minutes (± 5 per cent). Switch off the pump.

Unless otherwise prescribed in the patient instructions shake the inhaler for 5 seconds and discharge 1 delivery to waste. Switch on the pump to the apparatus. Prepare the inhaler for use according to the patient instructions, locate the mouthpiece end of the actuator in the adapter and discharge the inhaler into the apparatus, depressing the valve for a sufficient time to ensure a complete discharge. Wait for 5 seconds before removing the assembled inhaler from the adapter. Repeat the procedure. The number of discharges should be minimised, and typically would not be greater than 10. The number of discharges is sufficient to ensure an accurate and precise determination of the fine panicle dose. After the final discharge, wait for 5 seconds and then switch off the pump.

Dismantle the apparatus and recover the active substance as follows: remove the induction port and mouthpiece adapter from the apparatus and recover the deposited active substance into an aliquot of solvent. Open the impactor by releasing the handle and lifting the lid. Remove the cup tray, with the collection cups, and recover the active substance in each cup into an aliquot of solvent.

Using a suitable method of analysis, determine the quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine panicle dose (see Calculations).

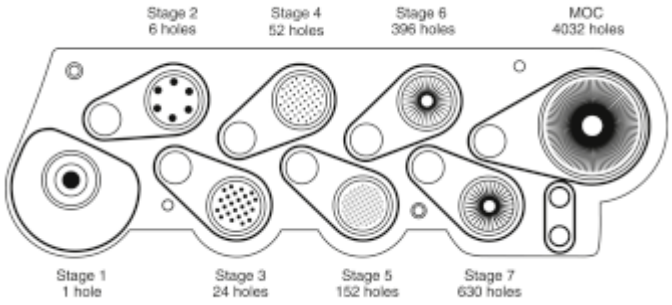


Fig. 13: Apparatus D: nozzle configuration

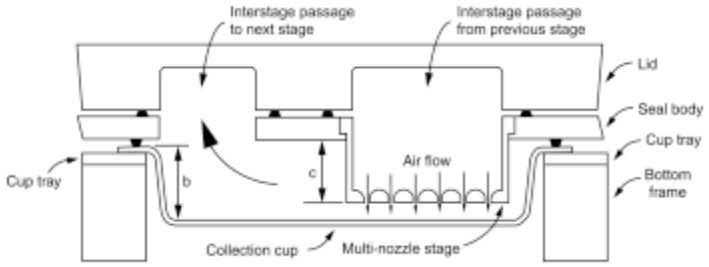


Fig. 14: Apparatus D: configuration of interstage passageways

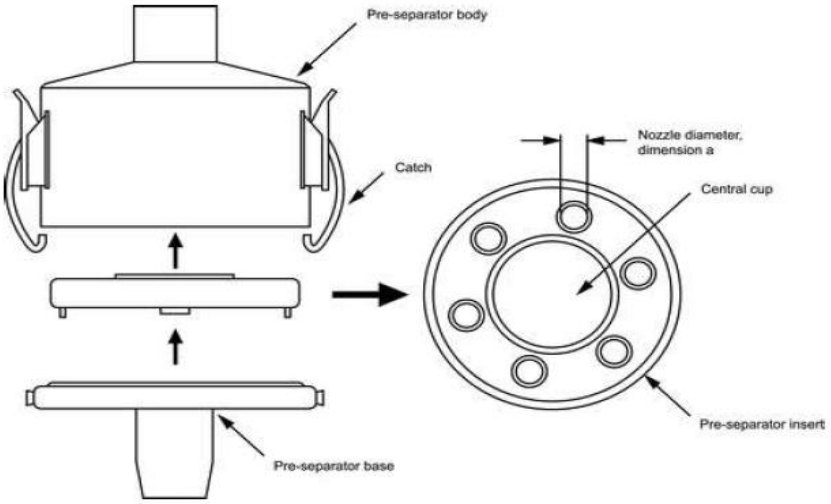


Fig. 15: Apparatus D: Pre-seperator configuration

Procedure for powder inhalers

Assemble the apparatus with the pre-separator (Fig. 15) Depending on the product characteristics, the pre-separator may be omitted, where justified.

Place cups into the apertures in the cup tray. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with the seal body attached and operate the handle to lock the impactor together so that the system is airtight.

When used, the pre-separator should be assembled as follows: assemble the pre-separator insert into the pre-separator base. Fit the pre-separator base to the impactor inlet. Add 15 ml of the solvent used for sample recovery to the central cup of the pre-separator insert. Place the pre-separator body on top of this assembly and close the 2 catches.

Connect an induction port with internal dimensions defined in Fig. 9 to the impactor inlet or pre-separator inlet. Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the inhaler, when inserted, lines up along the horizontal axis of the induction port. The front face of the inhaler mouthpiece must be flush with the front face of the induction port. When attached to the mouthpiece adapter, the inhaler is positioned in the same orientation as intended for use. Connect the apparatus to a flow system according to the scheme specified in Fig. 10 and Table 6.

Unless otherwise prescribed, conduct the test at the flow rate, Q_{out}, used in the test for uniformity of delivered dose drawing 4 liter of air from the mouthpiece of the inhaler and through the apparatus. Connect a flow meter to the induction port. Use a flow meter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the following expression:

$$Q_{out} = \frac{Q_{in} \text{ x} P_0}{P_0 - \Delta P}$$

Po = atmospheric pressure,
ΔP = pressure drop over the meter.

Adjust the flow control valve to achieve steady flow through the system at the required rate, Q_{out} (± 5 per cent). Ensure that critical flow occurs in the flow control valve by the procedure described for Apparatus D. Switch off the pump.

Prepare the powder inhaler for use according to the patient instructions. With the pump running and the 2-way solenoid valve closed, locate the mouthpiece of the inhaler in the mouthpiece adapter. Discharge the powder into the apparatus by opening the valve for the required time, T (± 5 per cent). Repeat the discharge sequence. The number of discharges should be minimised and typically would not be greater than 10. The number of discharges is sufficient to ensure an accurate and precise determination of fine particle dose.

Dismantle the apparatus and recover the active substance as follows: remove the induction port and mouthpiece adapter from the pre-separator, when used, and recover the deposited active substance into an aliquot of solvent. When used, remove the pre-separator from the impactor, being careful to avoid spilling the cup liquid into the impactor. Recover the active substance from the pre-separator.

Open the impactor by releasing the handle and lifting the lid. Remove the cup tray, with the collection cups, and recover the active substance in each cup into an aliquot of solvent.

Using a suitable method of analysis, determine the quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (see Calculations).

Calculations

Table 8. Calculations for Apparatus C. Use $q = \sqrt{(60/Q)}$, where Q is the test rate in liters per minute (Q_{out} for powder inhalers)

Cut-off diameter (µm)	**Mass of active substance deposited per discharge**	**Cumulative mass of active substance deposited per discharge**	**Cumulative fraction of active substance (per cent)**
d_4 = 1.7 X q	Mass from stage 5, m_5*	$C_4 = m_5$	$f_4 = (C_4/c)$ X 100
d_3 = 3.1 X q	Mass from stage 4, m_4	$C_3 = C_4 + m_4$	$f_3 = (C_3/c)$ X 100
d_3 = 6.8 X q	Mass from stage 3, m_3	$C_2 = C_3 + m_3$	$f_2 = (C_2/c)$ X 100
	Mass from stage 2, m_2	$C = C_2 + m_2$	100

* Stage 5 is the filter stage

Table 9. Calculations for Apparatus B when used at a flow rate of 28.3 litres per minutes

Cut-off diameter (µm)	**Mass of active substance deposited per discharge**	**Cumulative mass of active substance deposited per discharge**	**Cumulative fraction of active substance (per cent)**
d_7 = 0.4	Mass from stage 8, m_8	$C_7 = m_8$	$f_7 = (C_7/c)$ X 100
d_6 = 0.7	Mass from stage 7, m_7	$C_6 = C_7 + m_7$	$f_6 = (C_6/c)$ X 100
d_5 = 1.1	Mass from stage 6, m_6	$C_5 = C_6 + m_6$	$f_5 = (C_5/c)$ X 100
d_4 = 2.1	Mass from stage 5, m_5	$C_4 = C_5 + m_5$	$f_4 = (C_4/c)$ X 100
d_3 = 3.3	Mass from stage 4, m_4	$C_3 = C_4 + m_4$	$f_3 = (C_3/c)$ X 100
d_2 = 4.7	Mass from stage 3, m_3	$C_2 = C_3 + m_3$	$f_2 = (C_2/c)$ X 100
d_1 = 5.8	Mass from stage 2, m_2	$C_1 = C_2 + m_2$	$f_1 = (C_1/c)$ X 100

d_0 = 9.0	Mass from stage 1, m_1	$C_0 = C_1 + m_1$	$f_0 = (C_0/c)$ X 100
	Mass from stage 0, m_0	$C = C_0 + m_0$	100

Table 10. Calculations for Apparatus D. Use $q = (60/Q)^X$, where Q is the test flow rate in liters per minute, and x is listed in the table

Cut-off diameter (µm)	X	Mass of active substance deposited per discharge	Cumulative mass of active substance deposited per discharge	Cumulative fraction of active substance (per cent)
d_7 = 0.34 X q	0.67	Mass from MOC or terminal filter, m_8	$C_7 = m_8$	$F_7 = (C_7/c)$ X 100
d_6 = 0.55 X q	0.60	Mass from stage 7, m_7	$C_6 = C_7 + m_7$	$F_6 = (C_6/c)$ X 100
d_5 = 0.94 X q	0.53	Mass from stage 6, m_6	$C_5 = C_6 + m_6$	$F_5 = (C_5/c)$ X 100
d_4 = 1.66 X q	0.47	Mass from stage 5, m_5	$C_4 = C_5 + m_5$	$F_4 = (C_4/c)$ X 100
d_3 = 2.82 X q	0.50	Mass from stage 4, m_4	$C_3 = C_4 + m_4$	$F_3 = (C_3/c)$ X 100
d_2 = 4.46 X q	0.52	Mass from stage 3, m_3	$C_2 = C_3 + m_3$	$F_2 = (C_2/c)$ X 100
d_1 = 8.06 X q	0.54	Mass from stage 2, m_2	$C_1 = C_2 + m_2$	$F_1 = (C_1/c)$ X 100
		Mass from stage 1, m_1	$C = C_1 + m_1$	100

From the analysis of the solutions, calculate the mass of active substance deposited on each stage per discharge and the mass of active substance per discharge deposited in the induction port, mouthpiece adapter and when used, the pre-separator.

Starting at the final collection site (filter or MOC), derive a table of cumulative mass versus cut-off diameter of the respective stage (see Tables 8 for Apparatus C, 9 for Apparatus B, 10 for Apparatus D). Calculate by interpolation the mass of the active substance less than 5 µm. This is the Fine Particle Dose (FPD).

If necessary, and where appropriate (e.g., where there is a log-normal distribution), plot the cumulative fraction of active substance versus cut-off diameter (see Tables 8/10) on log probability paper, and use this plot to determine values for the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) as appropriate. Appropriate computational methods may also be used.

Preparations for Nebulisation: Characterisation

Products used for nebulisation and intended for pulmonary delivery are characterised using the following tests:
– Active substance delivery rate and total active substance delivered;
– Aerodynamic assessment of nebulised aerosols.
These tests standardise the approach given to the assessment of the dose that would be delivered to a patient but are not intended to provide assessment of the nebuliser device itself.

The mass- rather than the number-weighted size distribution is more appropriate to evaluate product performance. Indeed, active substance mass as a function of aerodynamic diameter is more indicative of therapeutic effect within the respiratory tract.

Active substance delivery rate and Total active substance delivered
These tests are performed to assess the rate of delivery to the patient and the total active substance delivered to the patient, using standardised conditions of volumetric flow rate. It is essential that breath-enhanced and breath-actuated nebulisers be evaluated by a breathing simulator, as the output of these types of device is highly dependent on inhalation flow rate. The methodology below describes the use of a standard breathing pattern defined for adults. Should a particular product for nebulisation only be indicated for paediatric (i.e. neonate, infant or child) use, and

then paediatric breathing pattern(s) must be used. Breathing patterns are used, rather than continuous flow rates, to provide a more appropriate measure of the mass of active substance that would be delivered to patients.
Active substance delivery rate and total active substance delivered are appropriate characteristics because they allow the mass delivered to be characterised in a standard way regardless of the nebuliser used. Accordingly, the test methodology described below allows that the mass of active substance delivered in the 1st period (typically 1 minute) is measured (consequently giving an assessment of active substance delivery rate) as well as capturing the total mass of active substance delivered.

Apparatus

Breathing simulator

A commercially available breathing simulator, which is able to generate the breathing profiles specified in Table 11, is used for the test. The breathing profile indicated for adults is used unless the medicinal product is specifically intended for use in paediatrics, where alternate patterns should be used, as indicated in Table 11.

Table 11 - Breathing simulator specifications

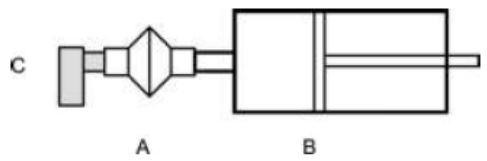
Item	Specification			
	Adult	**Neonate**	**Infant**	**Child**
Tidal volume	500 ml	25 ml	50 ml	155 ml
Frequency	15 cycles per minutes	40 cycles per minutes	30 cycles per minutes	25 cycles per minutes
Waveform	sinusoidal	sinusoidal	sinusoidal	sinusoidal
Inhalation/exhalation ratio	1:1	1:3	1:3	1:2

Filter system

A suitably validated low-resistance filter, capable of quantitatively collecting the aerosol and enabling recovery of the active substance with an appropriate solvent, is used for the test. The dead volume of the filter casing does not exceed 10 per cent of the tidal volume used in the breath simulation.

Method

Attach the filter (contained in the filter holder) (A) to the breath simulator (B) according to Fig. 16 Fill the nebuliser (C) with the volume of the medicinal product as specified in the patient instructions. Attach the mouthpiece of the nebuliser to the inhalation filter using a mouthpiece adapter if required, ensuring that connections are airtight. Make sure the nebuliser is positioned in the same orientation as intended for use; this may require tilting the breathing simulator and filter holder. Set the breathing simulator to generate the specified breathing pattern.



A. Inhalation filter and filter holder B. Breathing simulator C. Nebuliser

Fig. 16: Experimental set-up for breathing simulator testing

Start the breathing simulator then, at the beginning of an inhalation cycle, start the nebuliser. Operate the nebuliser for a defined initial time period. The time chosen, usually 60 ± 1 second, must allow sufficient active substance deposition on the inhalation filter to allow quantitative analysis. If the quantity of active substance deposited on the inhalation filter in 60 seconds is in sufficient for this analysis, the length of the time interval for aerosol collection can be increased. If the filter is soaked with the preparation, this time can be decreased. At the end of this initial period, stop the nebuliser.
Place a fresh filter and filter holder in position and continue until nebulisation ceases. Interrupt nebulisation and exchange filters if necessary, to avoid filter saturation.

Results

Using a suitable method of analysis, determine the mass of active substance collected on the filters and filter holders during each time interval. Determine the active substance delivery rate by dividing the mass of active substance collected on the first inhalation filter by the time interval used for collection. Determine the total mass of active substance delivered by summing the mass of active substance collected on all inhalation filters and filter holders.

Aerodynamic assessment of nebulised Aerosols

Nebulised products need to be size-characterised at flow rates lower than the range that is normally used for powder inhalers and metered-dose inhalers. A flow rate of 15 liter per minutes is recommended in the European standard because this value represents a good approximation to the mid-inhalation flow rate achievable by a tidally breathing healthy adult (500 ml tidal volume). Although low-angle laser light scattering instruments (laser diffractometers) can provide rapid sae-distribution measurements of nebuliser-generated aerosols, these techniques do not detect the active substance; rather they measure the size distribution of the droplets irrespective of their content. This may not be a problem with homogeneous solutions, but can result in significant error if the product to be nebulised is a suspension, or if droplet evaporation is significant as can be the case with certain nebuliser types. Cascade impactors enable the aerosol to be characterised unambiguously in terms of the mass of active substance as a function of aerodynamic diameter. Laser diffraction may be used if validated against a cascade impaction method.

Apparatus D a cascade impactor, has been calibrated at 15 litres per minutes specifically to meet the recommendation of the European standard, and is therefore used for this test. Determining mass balance in the same way as for powder inhalers and metered-dose inhalers is not straightforward, in that the dose is being captured as a continuous output, and hence is not included. As part of method development, recovery experiments must be performed to validate the method.

It is also recognised that the control of evaporation of droplets produced by nebulisers may be critical to avoid bias in the droplet size assessment process. Evaporation can be minimised by cooling the impactor to a temperature of about 5º, typically achieved by cooling the impactor in a refrigerator for about 90 minutes. Typically, at least after each day of use, the apparatus must be fully cleaned, including the inter-stage passageways, in view of the greater risk of corrosion caused by the condensation/accumulation of saline-containing droplets on inter-stage metalwork associated with cooling the impactor. It is recommended to dry all surfaces of the apparatus after each test, for example with compressed air. Note: the micro-orifice collector (MOC) should not be dried with compressed air.

Apparatus

A detailed description of Apparatus D and the induction port is contained in preparation for inhalation, and includes details of critical dimensions and the qualification process for the impactor (stage mensuration).

A back-up filter in addition to the micro-orifice collector (MOC) must be used to ensure quantitative recovery of active substance from the nebulised aerosol at the specified flow rate of 15 litres per minutes. The filter is located below the MOC (internal filter option) or a filter in holder, external to the impactor, is used to capture any fine droplets that pass beyond the last size fractionating stage.

A pre-separator is not used for testing nebuliser-generated aerosols.

Method validation

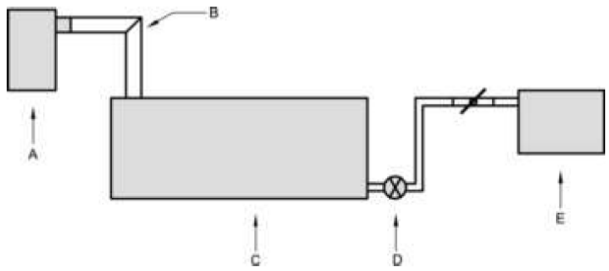
Impactor stage overloading

During method development and validation, it is important to confirm that the volume of liquid sampled from the nebuliser does not overload the impactor. Visual inspection of the collection surfaces on stages collecting most of the droplets may reveal streaking if overloading has occurred. This phenomenon is usually also associated with an increase in mass of active substance collected on the final stage and back-up filter. Reducing the sampling period (T_0) is the most effective way to avoid overloading in any given system, balancing overloading with analytical sensitivity.

Re-entrainment

Droplet bounce re-entrainment are less likely with nebuliser-produced droplets than with solid particles from inhalers and for that reason coating would not normally be required.

Method



A. Nebuliser B. Induction port C. Impactor(apparatus D) D. Flow control valve E. Vacuum source

Fig. 17: Apparatus D for measuring the size distribution of preparations for nebulisation

Pre-cool the assembled impactor and induction port in a refrigerator (set at about 5°) for not less than 90 minutes and start the determination within about 5 minutes of removal of the impactor from the refrigerator. Other methods that maintain the impactor at a constant temperature (for example, use of a cooling cabinet) can also be employed when validated.

Set up the nebuliser with a supply of driving gas (usually air or oxygen), or use a compressor, at the pressure and flow rate specified by the manufacturer of the nebuliser. Take precautions to ensure that the gas supply line does not become detached from the nebuliser when under pressure. Fill the nebuliser with the volume of the medicinal product as specified in the patient instructions.

Remove the impactor from the refrigerator. Attach the induction port to the impactor, and connect the outlet of the impactor/external filter to a vacuum source that is capable of drawing air through me system at 15 litres per minutes as specified in Fig. 17. Turn on the flow through the impactor.

Connect a flow meter, calibrated for the volumetric flow leaving the meter, to the induction port. Adjust the flow control valve located between the impactor and the vacuum source to achieve a steady flow through the system at 15 litres per minutes (± 5 per cent). Remove the flow meter.

Make sure the nebuliser is positioned in the same orientation as intended for use then attach the mouthpiece of the nebuliser to the induction port, using a mouthpiece adapter if required, ensuring that connections are airtight. Switch on the flow/compressor for the nebuliser. Sample for a predetermined time (T_0). Once determined, this time (T_0) must be defined and used in the analytical method for a particular medicinal product to ensure that mass fraction data can be compared. At the end of the sampling period, switch off the driving gas flow/ compressor to the nebuliser, remove the nebuliser from the induction port and switch off the flow from the vacuum source to the impactor.

Dismantle the impactor and, using a suitable method of analysis, determine the mass of active substance collected in the induction port, on each stage and on the back-up filter/external filter as described for Apparatus D. Add the mass of active substance collected in the MOC to that deposited on the back-up filter/external filter and treat as a single sample for the purpose of subsequent calculations.

Calculate the mass fraction ($F_{m,comp}$) of the active deposited on each component of the impactor, commencing with the induction port and proceeding in order through the impactor, using the following expression:

$$F_{m,comp} = \frac{m_{comp}}{M}$$

m_{comp} = mass associated with the components under evaluation;
M = total mass collected by the system.

Present $F_{m,comp}$ in order of location within the measurement equipment, beginning at the induction port and ending with the back-up filter of the impactor (Fig. 18). Where appropriate, $F_{m,comp}$ for adjacent stages of the impactor may be combined in order to report the mass fraction collected on a group of stages as a single value.

Determine the cumulative mass-weighed particle-size distribution of the aerosol size-fractionated by the impactor in accordance with the procedure given in inhalation preparation. Starting at the filter, derive a cumulative mass versus effective cut-off diameter of the respective stages (see Table 12 for the appropriate cut-off diameters at 15 litres per minutes). Plot the cumulative fraction of active substance versus cut-off diameter in a suitable format, for example logarithmic or log-probability format. Where appropriate, determine by interpolation the fraction either below a given size or between an upper and a lower size limit.

Table 12 - Cut-off sizes for Apparatus D at 15 litre per minutes

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

If necessary, and where appropriate, determine values for the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD), as appropriate.

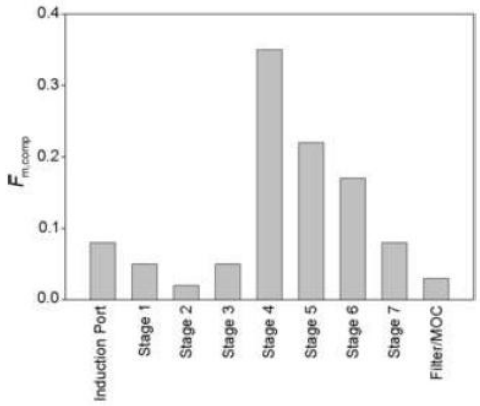


Fig. 18: Example of mass fraction of droplets presented in terms of location within the sampling system

Content of active ingredient on actuation of the valve test
The following test conditions are for use in preparations for inhalation. Specifically the methodology should be applied to pressurised inhalation products.

Content of active ingredient delivered by actuation of the valve
Remove the pressurised container from the actuator and remove all labels and markings which may be present on the container with a suitable solvent. Dry the container, replace in its actuator, shake for 30 seconds and prime the metering valve as follows. Discharge once to waste, wait for no less than 5 seconds and discharge again to waste. Remove the pressurised container from its actuator; clean the valve stem (internally and externally and the valve ferrule by washing with a suitable solvent. Dry the complete valve assembly using an air line fitted with an appropriate narrow jet to ensure that all solvent is removed from the inside of the valve stem.

Place a stainless steel base plate that has three legs and a central circular indentation with a hole about 1.5 mm in diameter in a small vessel suitable for shaking and add the volume of solvent specified in the monograph. The size of the vessel is such that when the pressurised inhalation is discharged into the specified volume of solvent as described below the discharge takes place not less than 25 mm below the surface of the solvent.

Shake the pressurised container for about 30 seconds and place it inverted in the vessel. Discharge 10 deliveries below the surface of the solvent actuating the valve at intervals of not less than 5 seconds, maintaining the pressurised container in the vertical plane and discharging the pressurised inhalation through the hole in the centre of the base plate. (It may be necessary because of the nature of the formulation to shake the pressurised container between each actuation of the valve; where this is the case shaking should be carried out without removing the pressurised container from its inverted position in the vessel). Remove the pressurised container, wash it with the specified solvent and dilute the combined solution and washing to the volume specified in the monograph. Determine the amount of active ingredient by the method described under the assay and calculate the amount delivered from each actuation of the valve. The result lies within the range for the content of active ingredient stated in the monograph.