transfer of the liquid contents from each of the stages, followed by dilution to a known volume. Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q = Q_{out}$ employed in the test by the formula:

$$D_{50,Q} = D_{50,Qn}(Qn / Q)^{1/2}$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, Q, employed in the test, and the subscript, n, refers to the nominal values determined when Q_n equals 60 L of air per minute. Thus, when Q equals 40 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40LPM} = 6.8\ \mu m \times (60/40)^{1/2} = 8.3\ \mu m.$$

Procedure— Proceed as directed in the *General Procedure* under *Apparatus 2*, except to use *Apparatus 4.*

Apparatus 5 for Dry Powder Inhalers—

Design— The design and assembly of *Apparatus 5* [5] are shown in *Figures 9, 9a, 9b, 9c,* and *9d.* The induction port, used to connect the device to an inhaler, is shown in *Figure 4a.* The device is a cascade impactor with seven stages and a micro-orifice collector (MOC). Over the design flow-rate range of 30 to 100 L per minute, the 50% efficiency cut-off diameters of the stages (D_{50} values) range between 0.24 µm to 11.7 µm, evenly spaced on a logarithmic scale. In the design flow-rate range, there are always at least five stages with D_{50} values between 0.5 µm and 6.5 µm. The collection efficiency curves for each stage are sharp and minimize overlap between stages. Material may be aluminum, stainless steel, or other suitable material.

The impactor layout has removable impaction cups with all the cups in one plane (*Figures 9 – 9c*). There are three 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 (shown in *Figures 9 – 9b*). Multiple nozzles are used at all but the first stage *(Figure 9c).* The flow passes through the impactor in a saw-tooth pattern.

Stage mensuration is performed periodically together with confirmation of other dimensions critical to the effective operation of the impactor. Critical dimensions are provided below in *Table 6.*

Table 6. Critical Dimensions for Apparatus 5 and 6

Description	Dimension (mm)
Preseparator (dimension a—see *Figure 9d*)	12.80 ± 0.05
Stage 1[1] Nozzle diameter	14.30 ± 0.05
Stage 2[1] Nozzle diameter	4.88 ± 0.04
Stage 3[1] Nozzle diameter	2.185 ± 0.02
Stage 4[1] Nozzle diameter	1.207 ± 0.01

Stage 5[1] Nozzle diameter	0.608 ± 0.01
Stage 6[1] Nozzle diameter	0.323 ± 0.01
Stage 7[1] Nozzle diameter	0.206 ± 0.01
MOC [1]	approximately 0.070
Cup Depth (Dimension b—see *Figure 9b*)	14.625 ± 0.10
Collection cup surface roughness	0.5 to 2 µm
Stage 1 Nozzle to seal body distance[2] —dimension c	0 ± 1.18
Stage 2 Nozzle to seal body distance[2] —dimension c	5.236 ± 0.736
Stage 3 Nozzle to seal body distance[2] —dimension c	8.445 ± 0.410
Stage 4 Nozzle to seal body distance[2] —dimension c	11.379 ± 0.237
Stage 5 Nozzle to seal body distance[2] —dimension c	13.176 ± 0.341
Stage 6 Nozzle to seal body distance[2] —dimension c	13.999 ± 0.071
Stage 7 Nozzle to seal body distance[2] —dimension c	14.000 ± 0.071
MOC Nozzle to seal body distance[2] —dimension c	14.429 – 14.571

[1] See *Figure 9c.*

[2] See *Figure 9b.*

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 identical to those defined in *Figure 4a* is connected to the impactor inlet. When necessary, with dry powder inhalers, a preseparator can be added to avoid overloading the first stage. This preseparator 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.

At a volumetric airflow rate of 60 L per minute (the assigned reference flow rate for cutoff-diameter calculations, Q_n), the cutoff-aerodynamic diameters $D_{50,Qn}$ of Stages 1 to 7 are 8.06, 4.46, 2.82, 1.66, 0.94, 0.55 and 0.34 µm, respectively. The apparatus contains a terminal micro-orifice collector (MOC) that for most formulations may eliminate the need for a final filter as determined by method validation. The MOC is an impactor nozzle plate and collection cup. The nozzle plate contains, nominally, 4032 jets, 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 L per minute, the MOC is capable of collecting 80% 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 containing a suitable after-filter

(glass fiber is often suitable).

Procedure— Assemble the apparatus with the preseparator *(Figure 9d),* unless experiments have shown that its omission does not result in increased interstage drug losses (>5%) or particle re-entrainment, in which case the preseparator may be omitted.

Place cups into the apertures in the cup tray. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. 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.

The preseparator may be assembled as follows: assemble the preseparator insert into the preseparator base; fit the preseparator base to the impactor inlet; add 15 mL of the solvent used for sample recovery to the central cup of the preseparator insert; place the preseparator body on top of this assembly; and close the two catches. [*Caution— Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (e.g., alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*]

Connect an induction port with internal dimensions as defined in *Figure 4a* either to the impactor inlet or to the preseparator inlet atop the cascade impactor *(Figure 9d).* 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 is flush with the front face of the induction port, producing an airtight seal. When attached to the mouthpiece adapter, the inhaler should be positioned in the same orientation as intended for use. Connect the apparatus to a flow system according to the scheme specified in *Figure 5.*

Unless otherwise prescribed, conduct the test at the flow rate used in the test for *Delivered-Dose Uniformity* drawing 4 L of air from the mouthpiece of the inhaler and through the apparatus. Connect a flowmeter to the induction port. 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 formula:

$$Q_{out} = Q_{in} P_0 / (P_0 - \Delta P)$$

where P_0 is the atmospheric pressure and ΔP is the pressure drop over the meter. Adjust the flow control valve to achieve steady flow through the system at the required rate, Q_{out} (±5%). Ensure that critical flow occurs in the flow-control valve by the procedure described for *Apparatus 2.* Adjust the timer controlling the operation of the two-way solenoid valve so that it opens the valve for the same duration, *T,* as used during testing

for *Delivered-Dose Uniformity*.

Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, *T* (±5%). After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the apparatus, and recover drug for analysis as follows: remove the induction port and mouthpiece adapter from the preseparator and extract the drug into an aliquot of solvent; if used, remove the preseparator from the impactor, without spilling the solvent into the impactor; and recover the active ingredient from all inner surfaces.

Open the impactor by releasing the handle and lifting the lid. Remove the cup tray, with the collection cups, and recover the active ingredient from each cup into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the mass of drug contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q = Q_{out}$ employed in the test by the formula:

$$D_{50,Q} = D_{50,Q_n}(Q_n / Q)^X, \quad \text{(Eq. 2)}$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, *Q*, employed in the test, and the subscript, *n*, refers to the nominal or reference value for Q_n = 60 L of air per minute (see *Table 7*). The values for the exponent, *x*, are listed in *Table 7*. Thus, when *Q* = 40 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40LPM} = 4.46\ \mu m \times (60/40)^{0.52} = 5.51\ \mu m.$$

Analyze the data as directed under *Data Analysis*.

Table 7. Cutoff Aerodynamic Diameter for Stages of *Apparatus 5* and *6*

Use Eq. 2 to calculate $D_{50,Q}$ for flow rates, *Q*, in the range 30 to 100 L per minute with Q_n = 60 L per minute.

Stage	D_{50,Q_n}	*x*
1	8.06	0.54
2	4.46	0.52

3	2.82	0.50
4	1.66	0.47
5	0.94	0.53
6	0.55	0.60
7	0.34	0.67

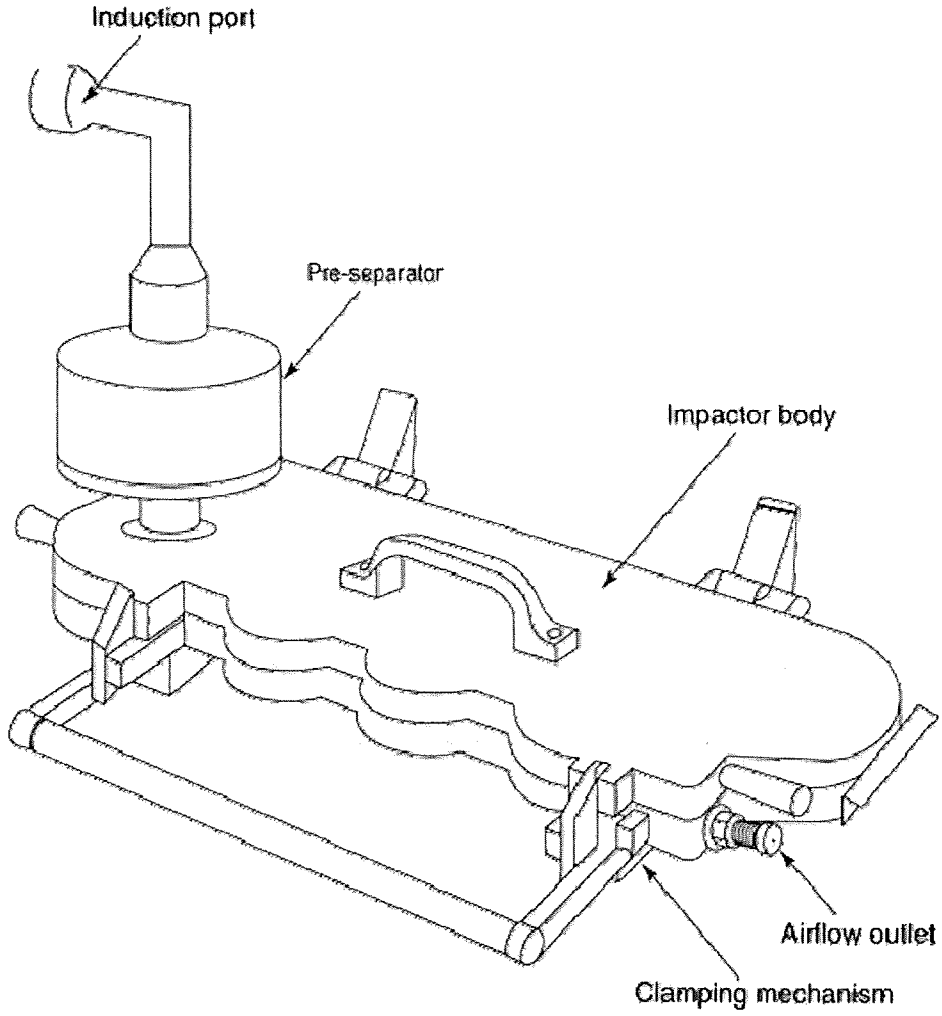

Fig. 9. Apparatus 5 (shown with the preseparator in place).

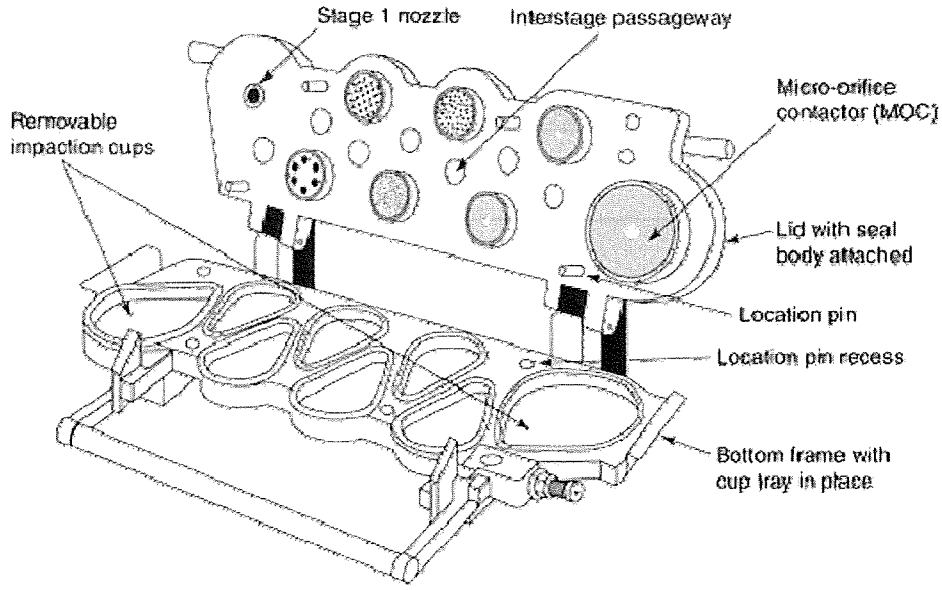

Fig. 9a. Components of *Apparatus 5*.

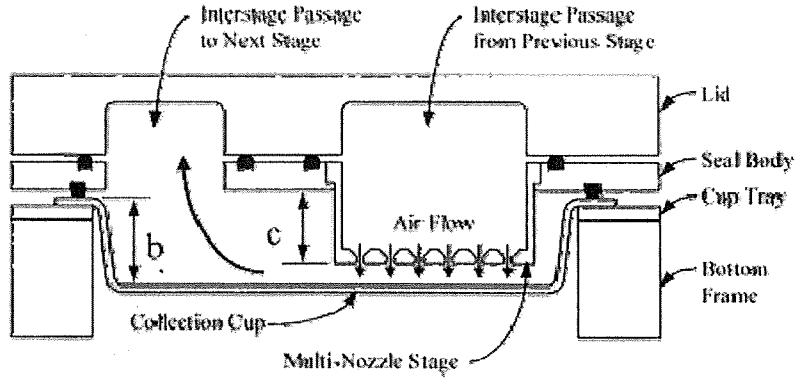

Fig. 9b. Layout of interstage passageways of *Apparatus 5*.

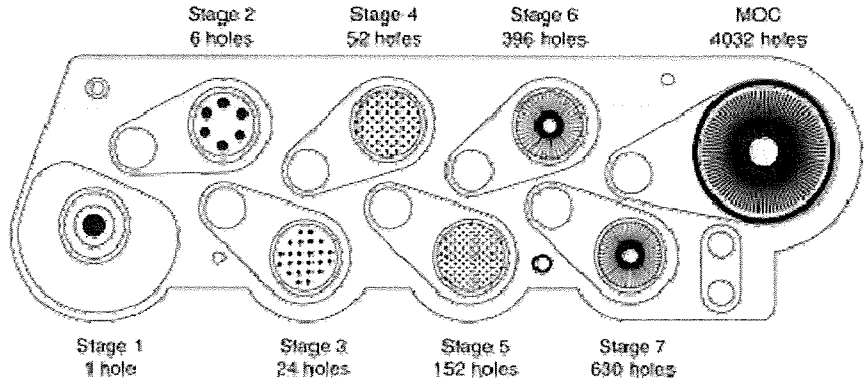

Fig. 9c. Nozzle configuration of *Apparatus 5*.

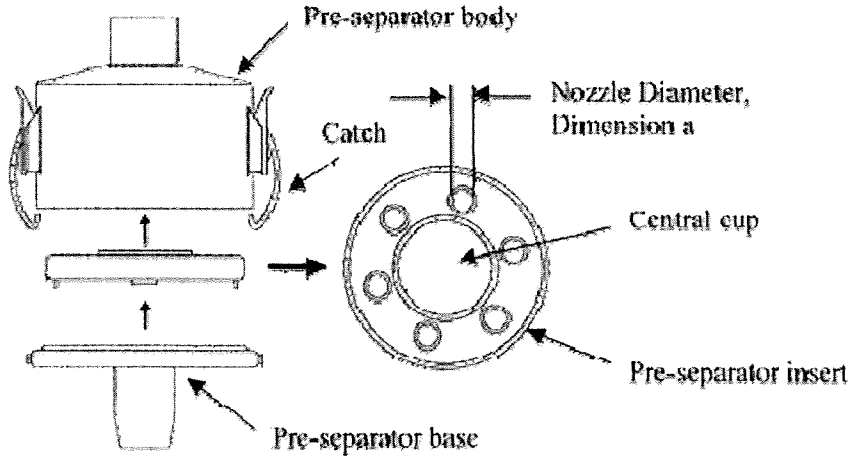

Fig. 9d. Pre-separator layout for *Apparatus 5.*

Apparatus 6 for Metered-Dose Inhalers—

Design— Apparatus 6 is identical to *Apparatus 5 (Figures 9-9d),* except that the preseparator is not to be used. Use this apparatus at a flow rate of 30 L per minute (±5%), unless otherwise prescribed in the individual monograph.

Procedure— Assemble the apparatus without the preseparator. Place cups into the apertures in the cup tray. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with 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 as defined in *Figure 4a* to the impactor inlet. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within ±5% of this flow rate. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and discharge one delivery to waste. With the vacuum pump running, insert the mouthpiece into the mouthpiece adapter, and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose.

Repeat until the required number of doses have been discharged. The number of minimum recommended doses discharged must be sufficient to ensure an accurate and

precise determination of *Aerodynamic Size Distribution.* [NOTE— The number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume.

Dismantle the apparatus, and recover the drug for analysis as follows: remove the induction port and mouthpiece adapter from the apparatus, and recover the deposited drug 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 extract the active ingredient in each cup into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the quantity of active ingredient contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of *Q* employed in the test by using Eq. 2 with values obtained from *Table 7.* Thus, when *Q* = 30 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,30LPM} = 4.46\ \mu m \times (60/30)^{0.52} = 6.40\ \mu m.$$

To analyze the data, proceed as directed under *Data Analysis.*

Data Analysis

This section describes the data analysis required to define the *Aerodynamic Size Distribution* of the drug output from the test inhaler, after the use of *Apparatus 1, 2, 3, 4, 5,* or *6.* Enter the data collected from *Apparatus 1, 2, 3, 4, 5,* or *6* in the table of mass summaries as shown in *Table 8.* Perform only those calculations specified in the individual monograph.

Table 8. Table of Mass Summaries for Analyses of Metered-Dose Inhalers and Dry Powder Inhalers

Mass	Apparatus 1		Apparatus 2		Apparatus 3[a]		Apparatus 4[b]		Apparatus 5[d]		Apparatus 6[d]	
Mouthpiece adapter	A_i	—	A_iA_i	—	A_i	—	A_i	—	A_i	—	A_i	—
Preseparator	—	—	—	—	A_P	—	—	—	A_P	—	—	—
Stage 0 of impactor	A_0	B_0	—	—	A_0	B_0	—	—	—	—	—	—
Stage 1 of impactor/impinger	A_1	B_1	A_1	—	A_1	B_1	A_1	—	A_1	B_1	A_1	B_1
Stage 2 of impactor/impinger	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2
Stage 3 of impactor/impinger	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3

Stage 4 of impactor/impinger	A_4	B_4	A_4	B_4	A_4	B_4	A_4	B_4	A_4	B_4	A_4	B_4
Stage 5 of impactor/impinger	A_5	B_5	A_5	B_5	A_5	B_5	—	—	A_5	B_5	A_5	B_5
Stage 6 of impactor/impinger	A_6	B_6	—	—	A_6	B_6	—	—	A_6	B_6	A_6	B_6
Stage 7 of impactor/impinger	A_7	B_7	—	—	A_7	B_7	—	—	A_7	B_7	A_7	B_7
Filter	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F
Sums of Masses	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c

[a] Stages 6 and 7 are omitted from *Apparatus 3* at airflow rates >60 L per minute.

[b] Stage 5 of *Apparatus 4* is the filter stage (see *Figure 8*).

[c] ΣA is the total drug mass recovered from the apparatus; ΣB is the mass of drug recovered from the impactor (*Apparatus 1*, *3*, *5* and *6*) or from the impactor stages beneath the uppermost stage (*Apparatus 2* and *4*).

[d] For *Apparatus 5* and *6*, values for the drug masses AF and BF refer to collections from the MOC, and/or the after-filter if used.

CALCULATIONS

Fine Particle Dose and Fine Particle Fraction— Calculate the total mass, ΣA, of drug delivered from the mouthpiece of the inhaler into the apparatus. Then calculate the total mass, *R,* of drug found on the stages of the apparatus and the filter that captured the drug in the fine particle size range appropriate for the particular drug being tested. The *Fine Particle Dose* is calculated by the formula:

$$R/n$$

where *R* is as stated above, and *n* is the number of doses discharged during the test. The *Fine Particle Fraction* that would be delivered from the inhaler is then calculated by the formula:

$$R/\Sigma A.$$

Cumulative Percentage (Cum%) of Drug Mass Less Than Stated Aerodynamic Diameter— Construct *Table 9* by dividing the mass of drug on the filter stage by ΣB (see *Table 8*). Multiply the quotient by 100, and enter this number as a percentage opposite the effective cutoff diameter of the stage immediately above it in the impactor or impinger stack. For *Apparatus 2* or *4,* use Equation 1 to calculate the stage cutoff diameters, $D_{50,Q}$, at the airflow rate, *Q,* employed during the test. For *Apparatus 5* and *6,* use Equation 2 with *Table 7.* For *Apparatus 1,* use the cutoff diameters quoted by the manufacturer. For *Apparatus 3,* present the data as cumulative percentages of mass on and below the stated stage, and avoid assigning values to stage cutoff diameters.

Repeat the calculation for each of the stages in the impactor or impinger stack, in reverse numerical order (largest to smallest stage number). For each stage, calculate the cumulative percentage of mass less than the stated aerodynamic diameter by adding the percentage of the mass on that stage to the total percentage from the stages below and entering the value opposite the effective cutoff diameter of the stage above it in the stack. Thus, the percentage of drug on the filter can be seen to have aerodynamic diameters less than the cutoff diameter of the stage above the filter, and the percentage on the filter plus the percentage on the stage above have diameters less than the cutoff diameter of the stage above that, and so on. Repeat the calculation for each of the remaining stages in reverse numerical order (see *Table 9*).

Table 9. Cumulative Percentage (Cum%) of Mass Less than the Stated Aerodynamic Diameter

	Apparatus 1		Apparatus 2		Apparatus 3[a]		Apparatus 4[b]		Apparatus 5		Apparatus 6	
Mass	Cum%[c]	D_{50}[d]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[e]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[d]
Filter		0.4		0.625		0.4		1.7		0.34		0.34
Stage 7	b	0.7	—	—	b	0.7	—	—	b	0.55	b	0.55
Stage 6	c	1.1	—	—	c	1.1	—	—	c	0.94	c	0.94
Stage 5	d	2.1	b	1.25	d	2.1	—	—	d	1.66	d	1.66
Stage 4	e	3.3	c	2.5	e	3.3	b	3.1	e	2.82	e	2.82
Stage 3	f	4.7	d	5.0	f	4.7	c	6.8	f	4.46	f	4.46
Stage 2	g	5.8	100	10.0	g	5.8	100	13.0	g	8.06	g	8.06
Stage 1	h	9.0	—	—	h	9.0	—	—	—	— —	—	—
Stage 0	100	—	—	—	100	—	—	—	100	—	100	—

[a] Stages 6 and 7 are omitted from *Apparatus 3* at flow rates >60 L per minute; thus, values for b and c should be omitted for *Apparatus 3*, where necessary.

[b] The filter stage in *Apparatus 4* is Stage 5 (see *Figure 8*).

[c] [(mass on stage / ΣB)×100] % + (total% of ΣB from stages below).

[d] The 50% cutoff diameter of the stage immediately above that indicated (e.g., for Stage 4, enter the cutoff diameter for Stage 3; for *Apparatus 2* or *4*, calculate as $D_{50,Q}$ from Eq.

1; for *Apparatus 5* or *6*, calculate as $D_{50,\,Q}$ from Eq. 2 using *Table 7*). Values entered in the Table are correct for *Apparatus 1, 2, 4, 5,* and *6* only when used at 28.3, 60.0, 60.0, 60.0, and 60.0 L per minute, respectively.

[e] The D_{50} values are only valid at a flow rate of 28.3 L per minute.

If necessary, and where appropriate, plot the percentage of mass less than the stated aerodynamic diameters, versus the aerodynamic diameter, $D_{50,Q}$, on log probability paper. Calculate the GSD by the equation:

$$GSD = \sqrt{\frac{Size\ X}{Size\ Y}}$$

Use these data and/or plot to determine values for MMAD and GSD etc., as appropriate and when necessary (see *Figure 10*).

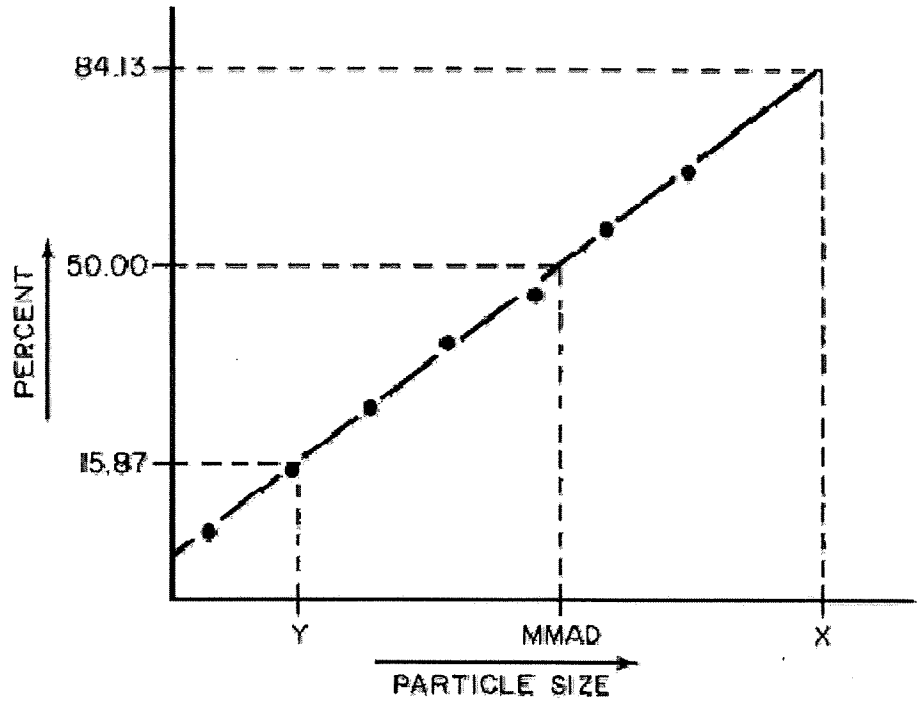

Fig. 10. Plot of cumulative percentage of mass less than stated aerodynamic diameter (probability scale) versus aerodynamic diameter (log scale).

[1] A suitable cascade impactor is available as Model Mk II from Thermo-Electron, 27 Forge Parkway, Franklin, MA 02038. The impactor is used without the preseparator. The inhaler is connected to the impactor via the induction port, atop the entrance cone shown in *Figure 4.* If an equivalent impactor is employed, the induction port in *Figure 4a* should be used, although the entrance cone (*Fig. 4b*) should be replaced with one to fit the impactor in question. Note that the internal surfaces of the induction port (*Fig. 4a*) are designed to fit flush with their counterparts in the entrance cone (*Fig. 4b*). This design avoids aerosol capture at the junction of the two pipes.

[2] The cascade impactor is available as the Model 160 Marple-Miller Impactor from MSP Corporation, Minneapolis, MN. The inhaler should be connected to the impactor via the induction port, shown in *Figure 4a.*

[3] The cascade impactor is available as the Andersen 1ACFM Non-Viable Cascade Impactor (Mark II) from Thermo-Electron, 27 Forge Parkway, Franklin, MA 02038. The impactor is used with the preseparator.

[4] The five-stage impinger is available from Copley Instruments, plc, Nottingham, UK. The inhaler should be connected to the impactor via the induction port, shown in *Fig. 4* and *Fig. 4a*

[5] The cascade impactor is available as the Next Generation Pharmaceutical Impactor from MSP Corporation, Minneapolis, MN.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	Kahkashan Zaidi, Ph.D. Senior Scientist 1-301-816-8269	(AER05) Aerosols05

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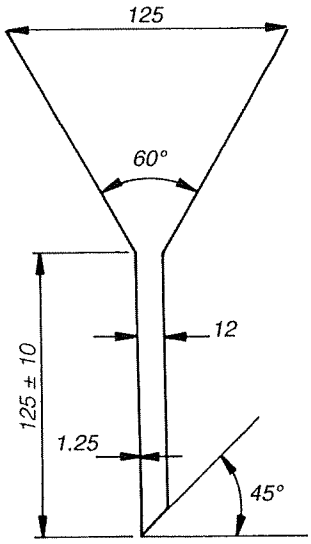

Figure 2.9.16.-2

Dimensions in millimetres

The volume is not less than the nominal volume in case of containers examined individually, or, in case of containers with a nominal volume of 2 ml or less, is not less than the sum of the nominal volumes of the containers taken collectively.

MULTI-DOSE CONTAINERS

For injections in multidose containers labelled to yield a specific number of doses of a stated volume, select one container and proceed as directed for single-dose containers using the same number of separate syringe assemblies as the number of doses specified.

The volume is such that each syringe delivers not less than the stated dose.

CARTRIDGES AND PREFILLED SYRINGES

Select 1 container if the nominal volume is 10 ml or more, 3 containers if the nominal volume is more than 3 ml and less than 10 ml, or 5 containers if the nominal volume is 3 ml or less. If necessary, fit the containers with the accessories required for their use (needle, piston, syringe) and transfer the entire contents of each container without emptying the needle into a dry tared beaker by slowly and constantly depressing the piston. Determine the volume in millilitres calculated as the mass in grams divided by the density.

The volume measured for each of the containers is not less than the nominal volume.

PARENTERAL INFUSIONS

Select one container. Transfer the contents into a dry measuring cylinder of such a capacity that the volume to be determined occupies at least 40 per cent of the nominal volume of the cylinder. Measure the volume transferred.

The volume is not less than the nominal volume.

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2.9.17. TEST FOR EXTRACTABLE VOLUME OF PARENTERAL PREPARATIONS

Suspensions and emulsions are shaken before withdrawal of the contents and before the determination of the density. Oily and viscous preparations may be warmed according to the instructions on the label, if necessary, and thoroughly shaken immediately before removing the contents. The contents are then cooled to 20-25 °C before measuring the volume.

SINGLE-DOSE CONTAINERS

Select 1 container if the nominal volume is 10 ml or more, 3 containers if the nominal volume is more than 3 ml and less than 10 ml, or 5 containers if the nominal volume is 3 ml or less. Take up individually the total contents of each container selected into a dry syringe of a capacity not exceeding 3 times the volume to be measured, and fitted with a 21-gauge needle not less than 2.5 cm in length. Expel any air bubbles from the syringe and needle, then discharge the contents of the syringe without emptying the needle into a standardised dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40 per cent of its graduated volume. Alternatively, the volume of the contents in millilitres may be calculated as the mass in grams divided by the density.

For containers with a nominal volume of 2 ml or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement provided that a separate, dry syringe assembly is used for each container. The contents of containers holding 10 ml or more may be determined by opening them and emptying the contents directly into the graduated cylinder or tared beaker.

01/2008:20918

2.9.18. 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 D and E). 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

The apparatus is shown in Figure 2.9.18.-1 (see also Table 2.9.18.-1).

Table 2.9.18.-1. – *Component specification for apparatus A in Figure 2.9.18.-1*

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	Modified round-bottomed flask	100 ml
	impingement	– *ground-glass inlet socket*	24/29
	chamber	– *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	Screwthread,	Plastic screw cap	28/13
	side-arm	Silicone rubber ring	28/11
	adaptor	PTFE washer	28/11
		Glass screwthread:	
		– *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 Figure 2.9.18.-1
		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	Conical flask	250 ml
	impingement chamber	– *ground-glass inlet socket*	24/29

* Dimensions in millimetres, unless otherwise stated.

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/min.

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 s switch on the nebuliser.

After 60 s, unless otherwise justified, switch off the nebuliser, wait for about 5 s 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.

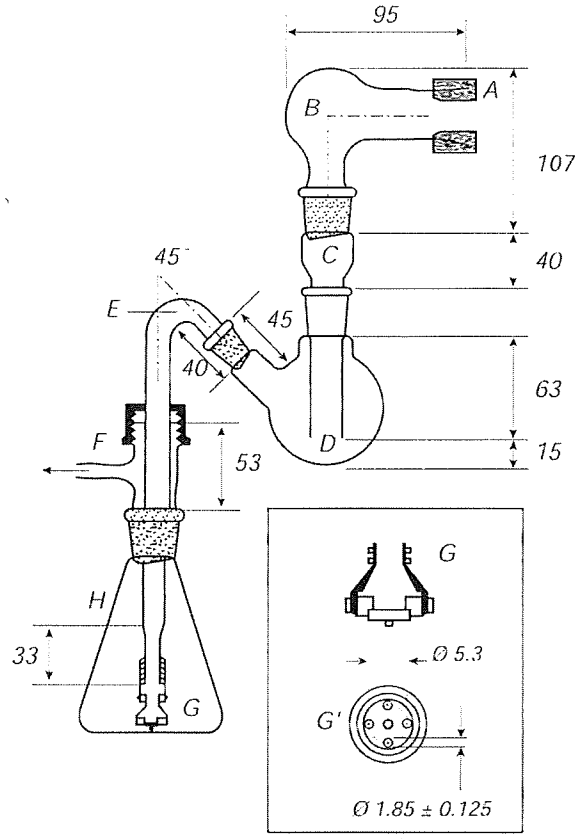


Figure 2.9.18.-1. – *Apparatus A: glass impinger*
Dimensions in millimetres (tolerances ± 1 mm unless otherwise prescribed)

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/min.

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

Shake for about 5 s, 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 s, 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 s 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/min.

Prepare the inhaler for use and locate the mouthpiece in the apparatus by means of a suitable adapter. Switch on the pump for 5 s. 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.

Fine particle dose and particle size distribution

APPARATUS C - 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 Figures 2.9.18.-4/6. An impaction stage comprises an upper horizontal metal partition wall (B) through which a metal inlet jet tube (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 Figure 2.9.18.-7) 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.

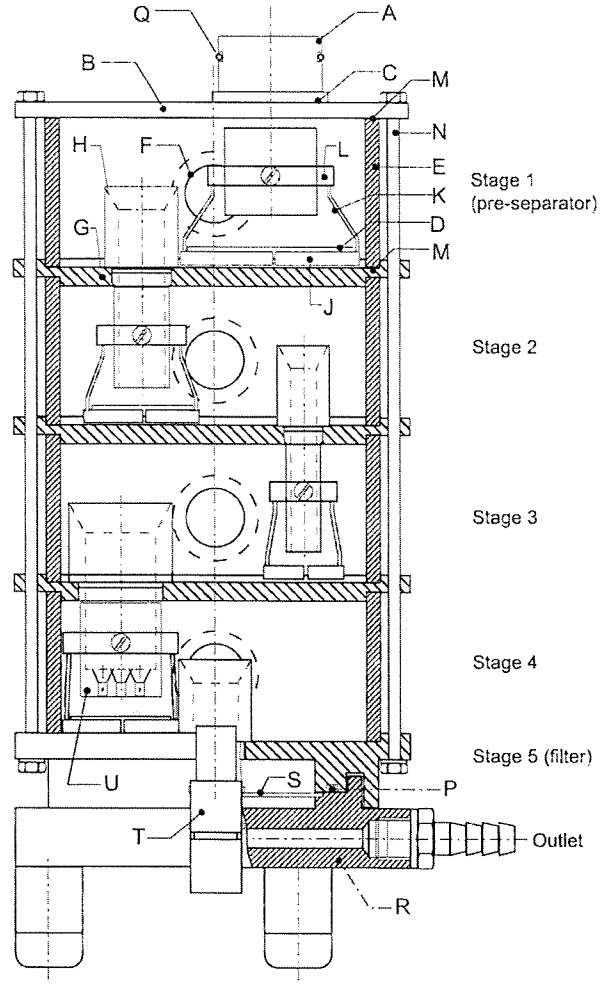


Figure 2.9.18.-4. – *Apparatus C: multi-stage liquid impinger*

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

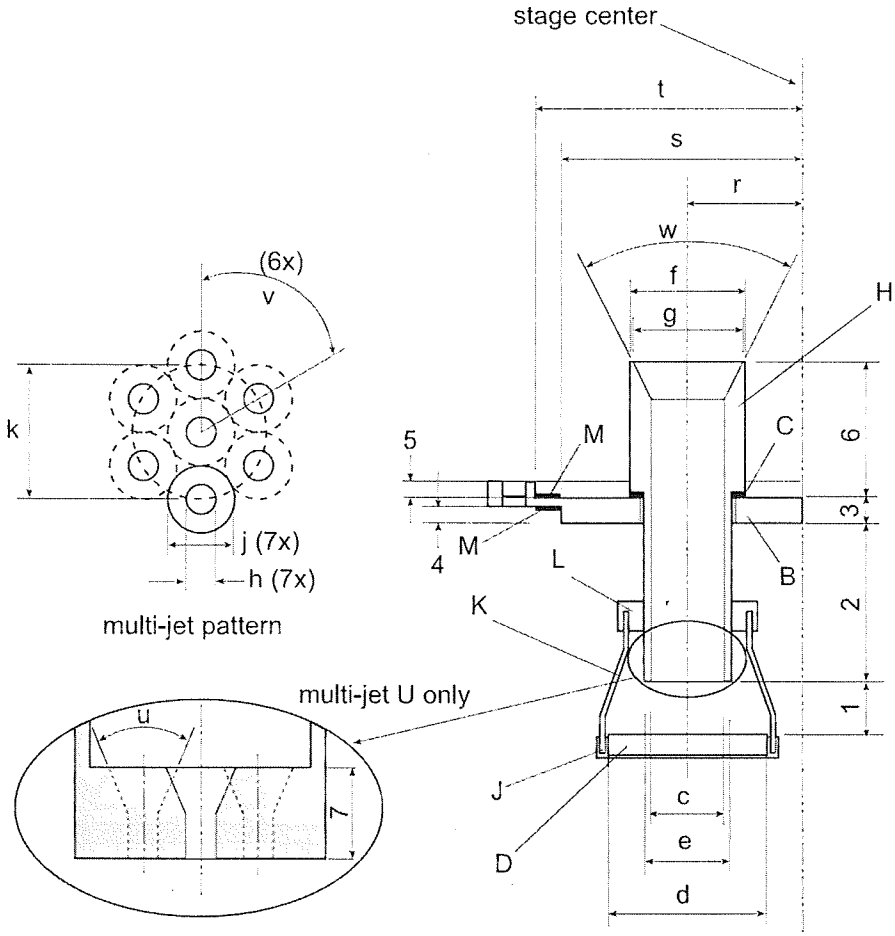


Figure 2.9.18.-5. – *Apparatus C: details of jet tube and impaction plate. Inserts show end of multi-jet tube U leading to stage 4. (Numbers and lowercase letters refer to Table 2.9.18.-3 and uppercase letters refer to Figure 2.9.18.-4).*

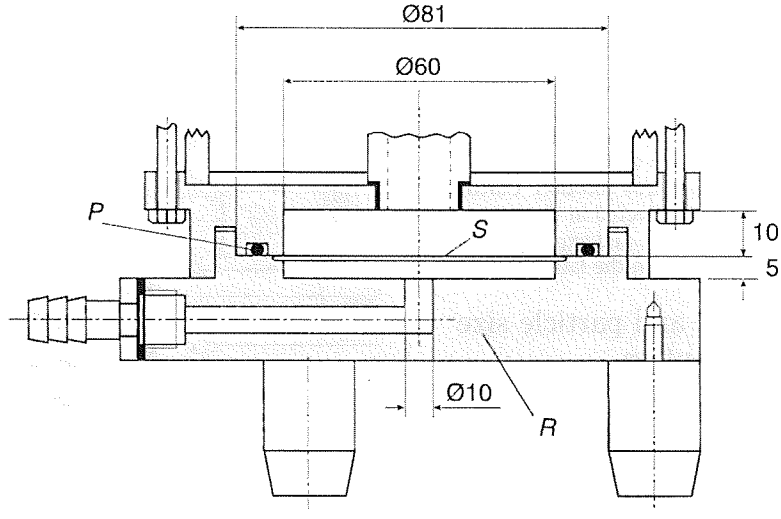


Figure 2.9.18.-6. – *Apparatus C: details of the filter stage (stage 5). Numbers refer to dimensions (Ø = diameter). Uppercase letters refer to Table 2.9.18.-2.*

Dimensions in millimetres unless otherwise stated

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/min (± 5 per cent). Switch off the pump.

Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 s 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 s 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 s 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 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 quantity of active substance contained in each of the aliquots of solvent.

Calculate the fine particle dose (see Calculations).

Table 2.9.18.-2. – *Component specification for apparatus C in Figures 2.9.18.-4/6*

Code*	Item	Description	Dimensions**
A,H	Jet tube	Metal tube screwed onto partition wall sealed by gasket (C), polished inner surface	see Figure 2.9.18.-5
B,G	Partition wall	Circular metal plate	
		– *diameter*	120
		– *thickness*	see Figure 2.9.18.-5
C	Gasket	e.g. PTFE	to fit jet tube
D	Impaction plate	Porosity 0 sintered-glass disk	
		– *diameter*	see Figure 2.9.18.-5
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* × *thickness*	66.34 × 2.62
Q	O-ring	Rubber O-ring	
		– *diameter* × *thickness*	29.1 × 1.6
R	Filter holder	Metal housing with stand and outlet	see Figure 2.9.18.-6
S	Filter support	Perforated sheet metal	
		– *diameter*	65
		– *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 Figure 2.9.18.-5

* Refers to Figure 2.9.18.-4.

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

Table 2.9.18.-3. – *Dimensions[1] of jet tube with impaction plate of apparatus C*

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[4]	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°	53°	53°	53°	53°
Angle	u	n.a.	n.a.	n.a.	45°	n.a.
Angle	v	n.a.	n.a.	n.a.	60°	n.a.

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

(2) Refer to Figure 2.9.18.-5

(3) Including gasket

(4) Relative centreline of stage compartment

n.a. = not applicable

Procedure for powder inhalers

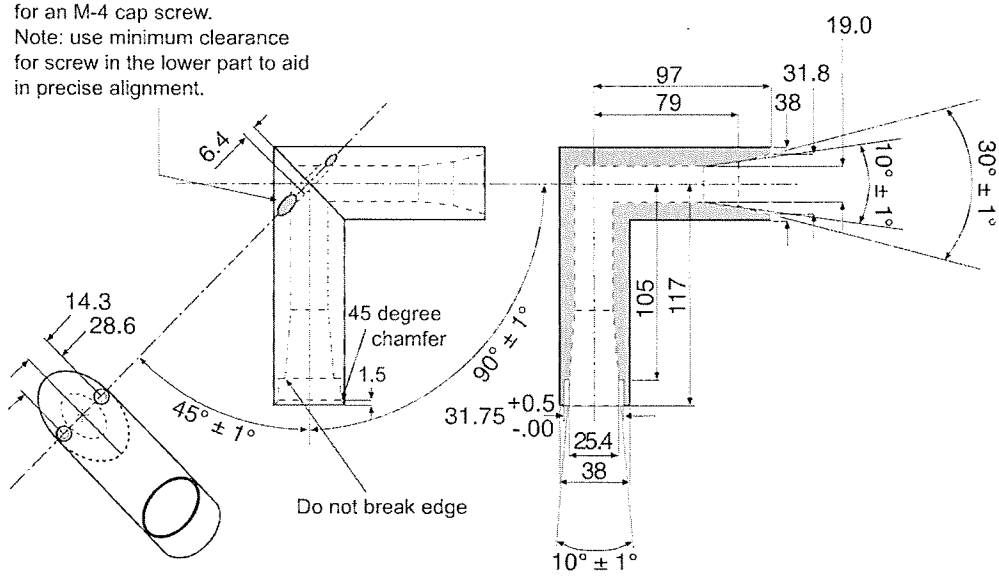
Place a suitable low resistance filter capable of quantitatively collecting the active substance in stage 5 and assemble the apparatus. Connect the apparatus to a flow system according to the scheme specified in Figure 2.9.18.-8 and Table 2.9.18.-4. Unless otherwise defined, conduct the test at the flow 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.

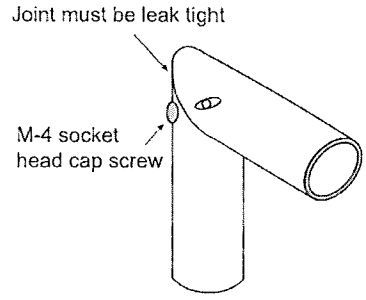
Connect a flowmeter to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the following expression:

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

P_0 = atmospheric pressure,

ΔP = pressure drop over the meter.





Isometric view of induction port

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° as shown.

(5) The inner bores and tapers should be smooth – surface roughness Ra approx. 0.4 µm.

(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 × 0.7 threads. There must be virtually no mismatch of the inner bores in the miter joint.

Figure 2.9.18.-7. – *Induction port*

Dimensions in millimetres unless otherwise stated

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.

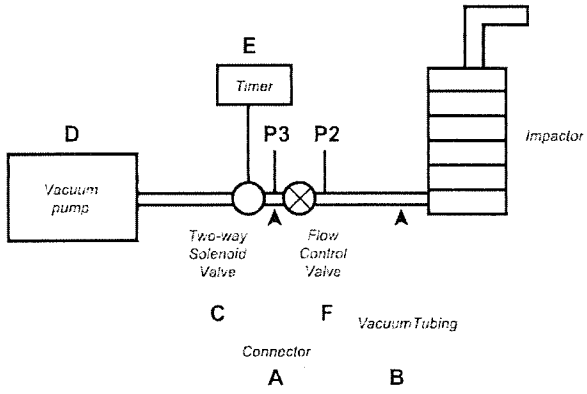


Figure 2.9.18.-8. – *Experimental set-up for testing powder inhalers*

Table 2.9.18.-4. – *Component specification for Figure 2.9.18.-8*

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, Bürkert 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 minimise 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.

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 Figure 2.9.18.-8). 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.

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 be 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 - 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 D are provided in Table 2.9.18.-5. 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 (Figure 2.9.18.-9) the entry cone of the impactor is connected to an induction port (see Figure 2.9.18.-7). 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.

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 Figure 2.9.18.-10. 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 2.9.18.-5. – *Critical dimensions for apparatus D*

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

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

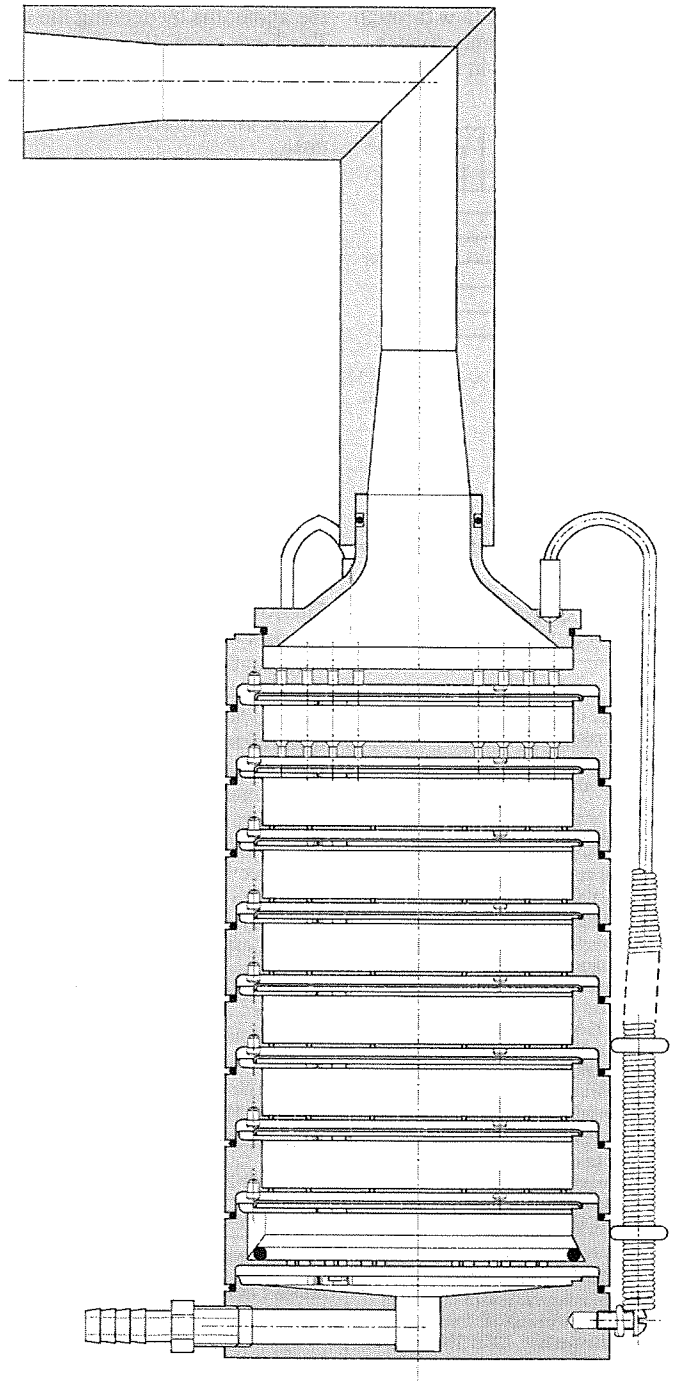


Figure 2.9.18.-9. – *Apparatus D: Andersen cascade impactor used for pressurised inhalers*

the apparatus, as measured at the inlet to the induction port, to 28.3 litres/min (± 5 per cent). Switch off the pump.

Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 s 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 s 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 s 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).