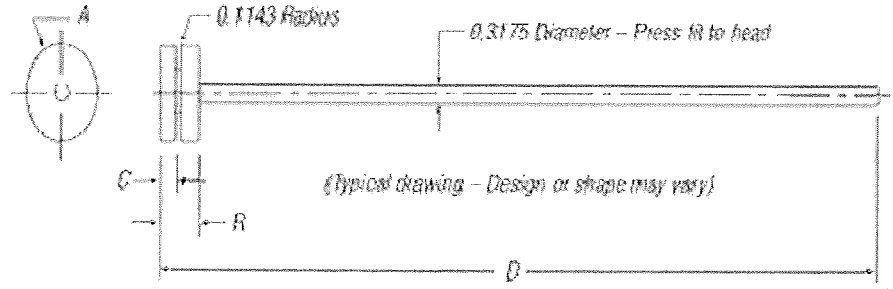


Dimensions are in centimeters

System[1]	HEAD				ROD		O-RING
	A (Diameter)	B	C	Material[2]	D	Material[3]	(not shown)
1.6cm²	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5cm²	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5cm²	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7cm²	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10cm²	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[1] Typical system sizes.
[2] SS/VT=Either stainless steel or virgin Teflon.
[3] SS/P=Either stainless steel or Plexiglas.

Fig. 3. Reciprocating Disk Sample Holder.[7]

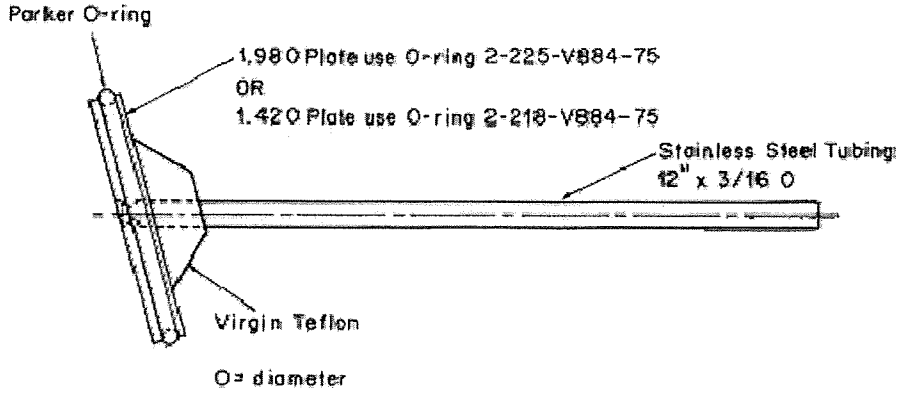


Fig. 4a. Transdermal System Holder—Angled Disk.

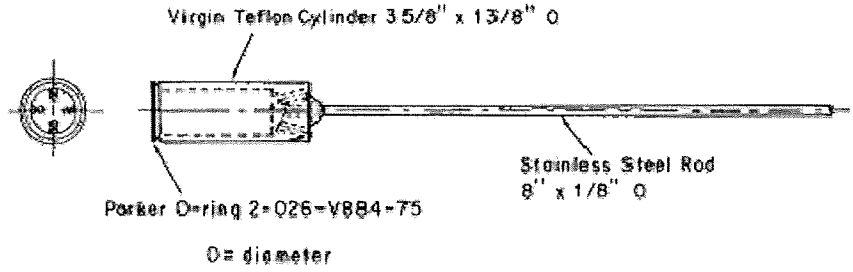


Fig. 4b. Transdermal System Holder—Cylinder.

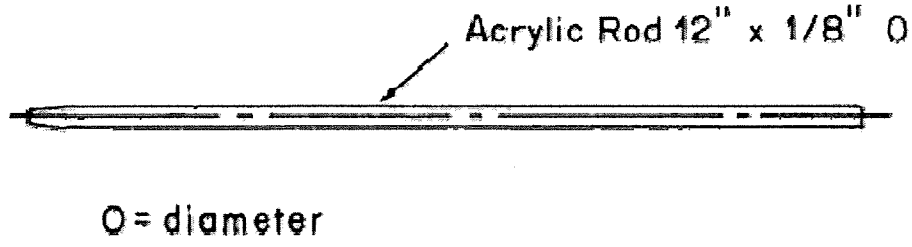
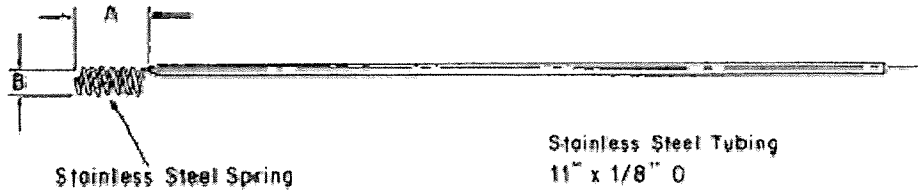


Fig. 4c. Oral Extended-Release Tablet Holder—Rod, Pointed for Gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O = diameter

Fig. 4d. Oral Extended-Release Tablet Holder—Spring Holder.

Dissolution Medium— Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* ⟨711⟩).

Sample Preparation A (Coated tablet drug delivery system)— Attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the end of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

Sample Preparation B (Transdermal drug delivery system)— Press the system onto a dry, unused piece of Cuprophan[4], nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitable sized sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

Sample Preparation C (Other drug delivery systems)— Attach each system to be tested to a suitable holder as described in the individual monograph.

Procedure— Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to temperature, *T*. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 2

cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (i.e., water in most cases) to correct for evaporative losses. Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

Interpretation— Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 2* under *Dissolution* ⟨ 711 ⟩ for coated tablet drug delivery systems, to *Acceptance Table 1* for transdermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either L_1 or L_2.

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[1] Disk assembly (stainless support disk) may be obtained from Millipore Corp., Ashley Rd., Bedford, MA 01730.

[2] A suitable device is the watchglass-patch-polytef mesh sandwich assembly available as the Transdermal Sandwich™ from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

[3] Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, or the equivalent.

[4] Use Cuprophan, Type 150 pm, 11 ± 0.5-µm thick, an inert, porous cellulosic material, which is available from Medicell International Ltd., 239 Liverpool Road, London NI ILX, England.

[5] The cylinder stirring element is available from Accurate Tool, Inc., 25 Diaz St., Stamford, CT 06907, or from VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513.

[6] The materials should not sorb, react with, or interfere with the specimen being tested.

[7] The reciprocating disk sample holder may be purchased from ALZA Corp., 1900 Charleston Road, P.O. Box 7210, Mt. View, CA 94039–7210 or VanKel Technology Group.

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

Topic/Question	Contact	Expert Committee
General Chapter	William E. Brown Senior Scientist 1-301-816-8380	(BPC05) Biopharmaceutics05

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川西資料4

QUALIFICATION AND VALIDATION

Due to the nature of the test method, quality by design is an important qualification aspect for *in vitro* dissolution test equipment. Any irregularities such as vibration or undesired agitation by mechanical imperfections are to be avoided.

Qualification of the dissolution test equipment has to consider the dimensions and tolerances of the apparatus. Critical test parameters, such as temperature and volume of dissolution medium, rotation speed or liquid flow rate, sampling probes and procedures have to be monitored periodically during the periods of use.

The performance of the dissolution test equipment may be monitored by testing a reference product which is sensitive to hydrodynamic conditions. Such tests may be performed periodically or continuously for comparative reasons with other laboratories.

During testing, critical inspection and observation are required. This approach is especially important to explain any out-lying results.

Validation of automated systems, whether concerning the sampling and analytical part or the dissolution media preparation and test performance, has to consider accuracy, precision, and the avoidance of contamination by any dilutions, transfers, cleaning and sample or solvent preparation procedures.

DISSOLUTION SPECIFICATIONS FOR ORAL DOSAGE FORMS

The dissolution specification is expressed as the quantity *Q* of the active substance as a percentage of the content stated on the product label, which is dissolved in a specified time frame.

Conventional-release dosage forms

Unless otherwise specified, the value of *Q* is 75 per cent. In most cases, when tested under reasonable and justified test conditions at least 75 per cent of the active substance is released within 45 min. Typically, one limit is specified to ensure that most of the active substance is dissolved within the pre-set time period.

In cases where a longer release time than that recommended above is justified, limits at 2 time intervals may be specified.

Prolonged-release dosage forms

A manufacturer's dissolution specification for prolonged-release dosage forms is normally expected to consist of 3 or more points. The first specification point is intended to prevent unintended rapid release of the active substance ('dose dumping'). It is therefore set after a testing period corresponding to a dissolved amount of typically 20 per cent to 30 per cent. The second specification point defines the dissolution pattern and so is set at around 50 per cent release. The final specification point is intended to ensure almost complete release which is generally understood as more than 80 per cent release.

Delayed-release dosage forms

A delayed-release dosage form may release the active substance(s) fractionally or totally according to the formulation design when tested in different dissolution media, e.g. in increasing pH conditions. Dissolution specifications have, therefore, to be decided from case to case.

Gastro-resistant dosage forms require at least 2 specification points in a sequential test and 2 different specifications in a parallel test. In a sequential test, the first specification point is set after 1 h or 2 h in acidic medium and the second one at a pre-set time period of testing in an adequate buffer solution (preferably pH 6.8). Unless otherwise specified, the value of *Q* is 75 per cent.

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2.9.4. DISSOLUTION TEST FOR TRANSDERMAL PATCHES

This test is used to determine the dissolution rate of the active ingredients of transdermal patches.

1. DISK ASSEMBLY METHOD

Equipment. Use the paddle and vessel assembly from the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*) with the addition of a stainless steel disk assembly (SSDA) in the form of a net with an aperture of 125 µm (see Figure 2.9.4.-1).

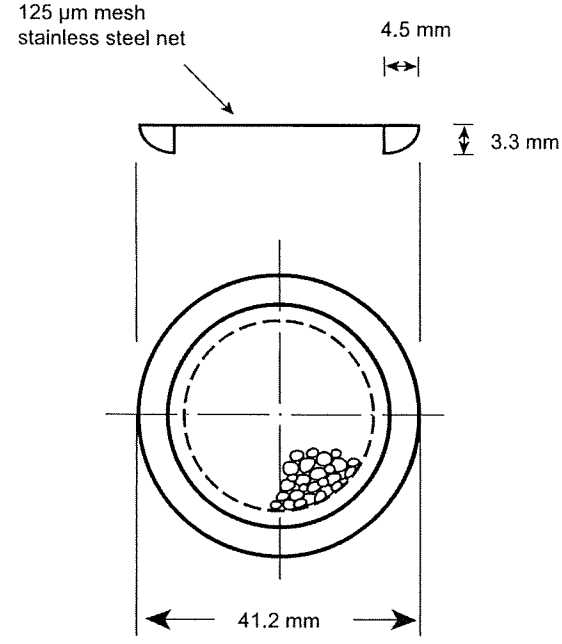

Figure 2.9.4.-1. – *Disk assembly*

The SSDA holds the system at the bottom of the vessel and is designed to minimise any dead volume between the SSDA and the bottom of the vessel. The SSDA holds the patch flat, with the release surface uppermost and parallel to the bottom of the paddle blade. A distance of 25 ± 2 mm between the bottom of the paddle blade and the surface of the SSDA is maintained during the test (see Figure 2.9.4.-2). The temperature is maintained at 32 ± 0.5 °C. The vessel may be covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Apply the patch to the SSDA, ensuring that the release surface of the patch is as flat as possible. The patch may be attached to the SSDA by a prescribed adhesive or by a strip of a double-sided adhesive tape. The adhesive or tape are previously tested for the absence of interference with the assay and of adsorption of the active ingredient(s). Press the patch, release surface facing up, onto the side of the SSDA made adhesive. The applied patch must not overlap the borders of the SSDA. For this purpose and provided that the preparation is homogeneous and uniformly spread on the outer covering, an appropriate and exactly measured piece of the patch

may be cut and used for testing the dissolution rate. This procedure may also be necessary to achieve appropriate sink conditions. This procedure must not be applied to membrane-type patches. Place the patch mounted on the SSDA flat at the bottom of the vessel with the release surface facing upwards. Immediately rotate the paddle at 100 r/min, for example. At predetermined intervals, withdraw a sample from the zone midway between the surface of the dissolution medium and the top of the blade, not less than 1 cm from the vessel wall.

Perform the assay on each sample, correcting for any volume losses, as necessary. Repeat the test with additional patches.

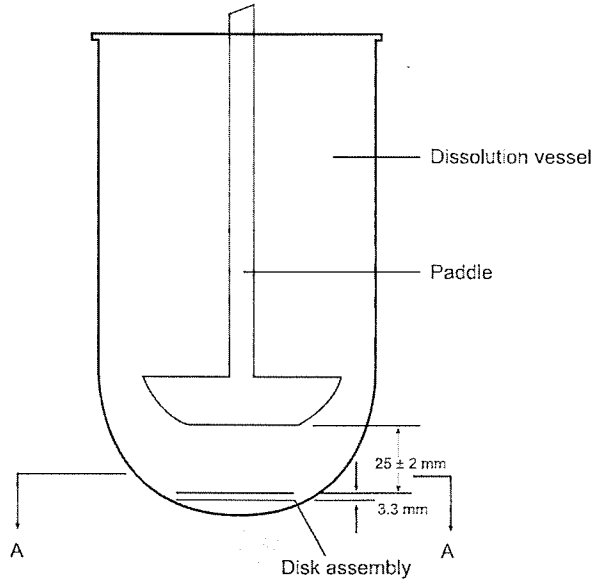

Figure 2.9.4.-2. – *Paddle and disk*

2. CELL METHOD

Equipment. Use the paddle and vessel assembly from the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*) with the addition of the extraction cell (*cell*).

The *cell* is made of chemically inert materials and consists of a *support*, a *cover* and, if necessary, a *membrane* placed on the patch to isolate it from the medium that may modify or adversely affect the physico-chemical properties of the patch (see Figure 2.9.4.-3).

Support. The central part of the support forms a cavity intended to hold the patch. The cavity has a depth of 2.6 mm and a diameter that is appropriate to the size of the patch to be examined. The following diameters can be used: 27 mm, 38 mm, 45 mm, 52 mm, corresponding to volumes of 1.48 ml, 2.94 ml, 4.13 ml, 5.52 ml, respectively.

Cover. The cover has a central opening with a diameter selected according to the size of the patch to be examined. The patch can thus be precisely centred, and its releasing surface limited. The following diameters may be used: 20 mm, 32 mm, 40 mm, 50 mm corresponding to areas of 3.14 cm^2, 8.03 cm^2, 12.56 cm^2, 19.63 cm^2, respectively. The cover is held in place by nuts screwed onto bolts projecting from the support. The cover is sealed to the support by a rubber ring set on the reservoir.

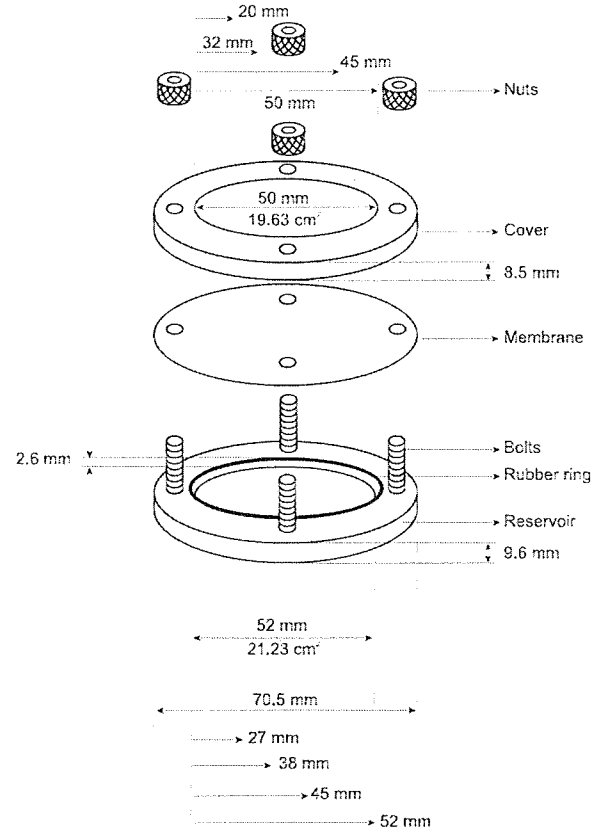

Figure 2.9.4.-3. – *Extraction cell*

Extraction cell. The *cell* holds the patch flat, with the release surface uppermost and parallel to the bottom of the paddle blade. A distance of 25 ± 2 mm is maintained between the paddle blade and the surface of the patch (see Figure 2.9.4.-4). The temperature is maintained at 32 ± 0.5 °C. The vessel may be covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Precisely centre the patch in the *cell* with the releasing surface uppermost. Close the *cell*, if necessary applying a hydrophobic substance (for example, petrolatum) to the flat surfaces to ensure the seal, and ensure that the patch stays in place. Introduce the cell flat into the bottom of the vessel with the cover facing upwards. Immediately rotate the paddle, at 100 r/min for example. At predetermined intervals, withdraw a sample from the zone midway between the surface of the dissolution medium and the top of the paddle blade, not less than 1 cm from the vessel wall.

Perform the assay on each sample, correcting for any volume losses, as necessary. Repeat the test with additional patches.

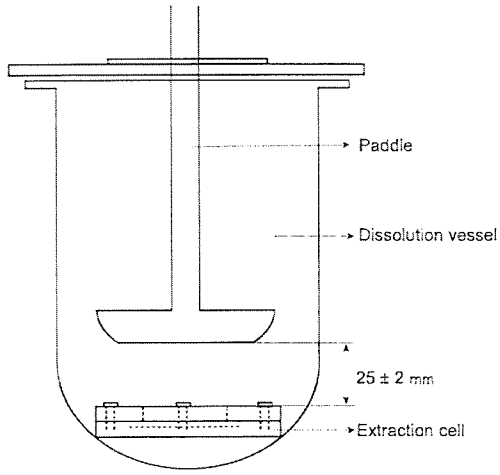

Figure 2.9.4.-4. – *Paddle over extraction cell*

3. ROTATING CYLINDER METHOD

Equipment. Use the assembly of the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*). Replace the paddle and shaft with a stainless steel cylinder stirring element (*cylinder*) (see Figure 2.9.4.-5). The patch is placed on the *cylinder* at the beginning of each test. The distance between the inside bottom of the vessel and the *cylinder* is maintained at 25 ± 2 mm during the test. The temperature is maintained at 32 ± 0.5 °C. The vessel is covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Remove the protective liner from the patch and place the adhesive side on a piece of suitable inert porous membrane that is at least 1 cm larger on all sides than the patch. Place the patch on a clean surface with the membrane in contact with this surface. Two systems for adhesion to the *cylinder* may be used:

- apply a suitable adhesive to the exposed membrane borders and, if necessary, to the back of the patch,
- apply a double-sided adhesive tape to the external wall of the *cylinder*.

Using gentle pressure, carefully apply the non-adhesive side of the patch to the *cylinder*, so that the release surface is in contact with the dissolution medium and the long axis of the patch fits around the circumference of the *cylinder*.

The system for adhesion used is previously tested for absence of interference with the assay and of adsorption of the active ingredient(s).

Place the *cylinder* in the apparatus, and immediately rotate the *cylinder* at 100 r/min, for example. At determined intervals, withdraw a sample of dissolution medium from a zone midway between the surface of the dissolution medium and the top of the rotating *cylinder*, and not less than 1 cm from the vessel wall.

Perform the assay on each sample as directed in the individual monograph, correcting for any volume withdrawn, as necessary. Repeat the test with additional patches.

Interpretation. The requirements are met if the quantity of active ingredient(s) released from the patch, expressed as the amount per surface area per time unit, is within the prescribed limits at the defined sampling times.

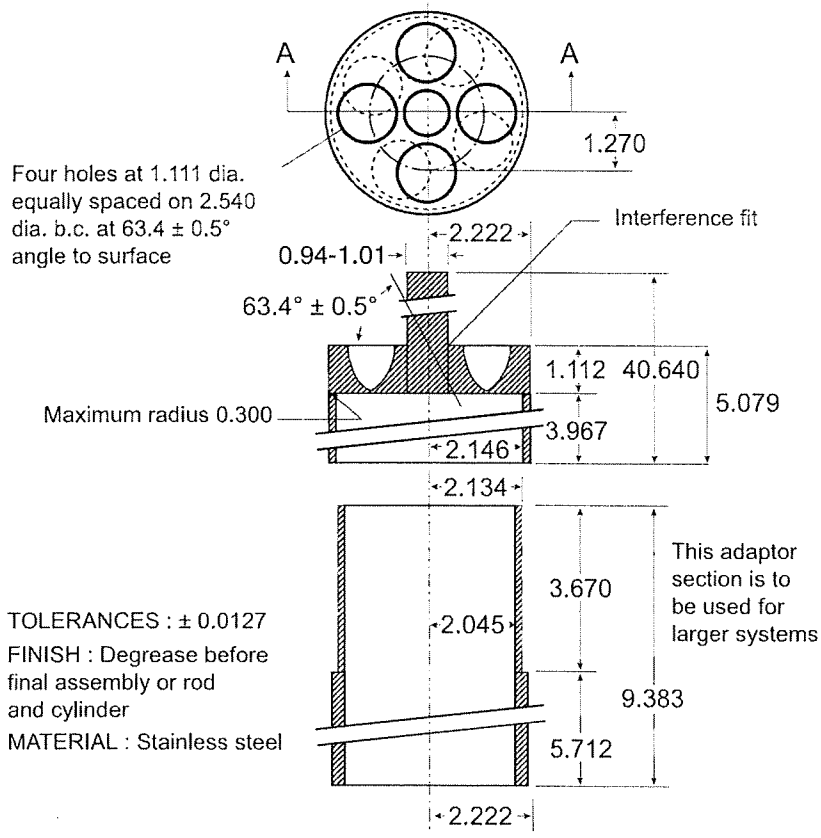

Figure 2.9.4.-5. – *Cylinder stirring element*
Dimensions in centimetres

川西資料5

〈601〉 AEROSOLS, NASAL SPRAYS, METERED-DOSE INHALERS, AND DRY POWDER INHALERS

This general chapter contains test methods for propellants, pressurized topical aerosols, nasal sprays, metered-dose inhalers, and propellant-free dry powder inhalers used to aerosolize, or to aerosolize and meter, doses of powders for inhalation. Apply these methods, where indicated, in the testing of the appropriate dosage forms.

PROPELLANTS

Caution— Hydrocarbon propellants are highly flammable and explosive. Observe precautions and perform sampling and analytical operations in a well-ventilated fume hood.

General Sampling Procedure

This procedure is used to obtain test specimens for those propellants that occur as gases at about 25° and that are stored in pressurized cylinders. Use a stainless steel sample cylinder equipped with a stainless steel valve and having a capacity of not less than 200 mL and a pressure rating of 240 psi or more. Dry the cylinder with the valve open at 110° for 2 hours, and evacuate the hot cylinder to less than 1 mm of mercury. Close the valve, cool, and weigh. Connect one end of a charging line tightly to the propellant container and the other end loosely to the sample cylinder. Carefully open the propellant container, and allow the propellant to flush out the charging line through the loose connection. Avoid excessive flushing, which causes moisture to freeze in the charging line and connections. Tighten the fitting on the sample cylinder, and open the sample cylinder valve, allowing the propellant to flow into the evacuated cylinder. Continue sampling until the desired amount of specimen is obtained, then close the propellant container valve, and finally close the sample cylinder valve. [*Caution— Do not overload the sample cylinder; hydraulic expansion due to temperature change can cause overloaded cylinders to explode.*] Again weigh the charged sample cylinder, and calculate the weight of the specimen.

Approximate Boiling Temperature

Transfer a 100-mL specimen to a tared, pear-shaped, 100-mL centrifuge tube containing a few boiling stones, and weigh. Suspend a thermometer in the liquid, and place the tube in a medium maintained at a temperature of 32° above the expected boiling temperature. When the thermometer reading becomes constant, record as the boiling temperature the thermometer reading after at least 5% of the specimen has distilled. Retain the remainder of the specimen for the determination of *High-Boiling Residues*.

High-Boiling Residues, Method I

Allow 85 mL of the specimen to distill as directed in the test for *Approximate Boiling Temperature*, and transfer the centrifuge tube containing the remaining 15 mL of specimen to a medium maintained at a temperature 10° above the boiling temperature. After 30 minutes, remove the tube from the water bath, blot dry, and weigh. Calculate the weight of the residue.

High-Boiling Residues, Method II

Prepare a cooling coil from copper tubing (about 6 mm outside diameter × about 6.1 m long) to fit into a vacuum-jacketed flask. Immerse the cooling coil in a mixture of dry ice and acetone in a vacuum-jacketed flask, and connect one end of the tubing to the propellant sample cylinder. Carefully open the sample cylinder valve, flush the cooling coil with about 50 mL of the propellant, and discard this portion of liquefied propellant. Continue delivering liquefied propellant from the cooling coil, and collect it in a previously chilled 1000-mL sedimentation cone until the cone is filled to the 1000-mL mark. Allow the propellant to evaporate, using a warm water bath maintained at about 40° to reduce evaporating time. When all of the liquid has evaporated, rinse the sedimentation cone with two 50-mL portions of pentane, and combine the rinsings in a tared 150-mL evaporating dish. Transfer 100 mL of the pentane solvent to a second tared 150-mL evaporating dish, place both evaporating dishes on a water bath, evaporate to dryness, and heat the dishes in an oven at 100° for 60 minutes. Cool the dishes in a desiccator, and weigh. Repeat the heating for 15-minute periods until successive weighings are within 0.1 mg, and calculate the weight of the residue obtained from the propellant as the difference between the weights of the residues in the two evaporating dishes.

Water Content

Proceed as directed under *Water Determination* ⟨921⟩, with the following modifications: (a) Provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder. (b) Dilute the *Reagent* with anhydrous methanol to give a water equivalence factor of between 0.2 and 1.0 mg per mL; age this diluted solution for not less than 16 hours before standardization. (c) Obtain a 100-g specimen as directed under *General Sampling Procedure*, and introduce the specimen into the titration vessel through the gas dispersion tube at a rate of about 100 mL of gas per minute; if necessary, heat the sample cylinder gently to maintain this flow rate.

Other Determinations

For those aerosols that use propellants, perform the tests specified in the individual *NF* propellant monographs.

AEROSOLS

Because leaching of extractable substances into pressurized formulations should be minimized, valve materials and other components that are in contact with the product meet the requirements under *Elastomeric Closures for Injections* ⟨ 381 ⟩ (Note that under *Physicochemical Test Procedures* in ⟨ 381 ⟩ the directions for preparing a sample require pre-extraction, which may cause an underestimate of the amount of extractables from a given component.) See also *Aerosols* under *Pharmaceutical Dosage Forms* ⟨ 1151 ⟩.

TOPICAL AEROSOLS

The following tests are applicable to topical aerosols containing drug, in suspension or solution, packaged under pressure, and released upon activation of an appropriate valve system.

Delivery Rate and Delivered Amount

Perform these tests only on containers fitted with continuous valves.

Delivery Rate— Select not fewer than four aerosol containers, shake, if the label includes this directive, remove the caps and covers, and actuate each valve for 2 to 3 seconds. Weigh each container accurately, and immerse in a constant-temperature bath until the internal pressure is equilibrated at a temperature of 25° as determined by constancy of internal pressure, as directed under the *Pressure Test* below. Remove the containers from the bath, remove excess moisture by blotting with a paper towel, shake, if the label includes this directive, actuate each valve for 5.0 seconds (accurately timed by use of a stopwatch), and weigh each container again. Return the containers to the constant-temperature bath, and repeat the foregoing procedure three times for each container. Calculate the average *Delivery Rate,* in g per second, for each container.

Delivered Amount— Return the containers to the constant-temperature bath, continuing to deliver 5 second actuations to waste, until each container is exhausted. [NOTE— Ensure that sufficient time is allowed between each actuation to avoid significant canister cooling.] Calculate the total weight loss from each container. This is the *Delivered Amount.*

Pressure Test

Perform this test only on topical aerosols fitted with continuous valves.

Select not fewer than four aerosol containers, remove the caps and covers, and immerse in a constant-temperature bath until the internal pressure is constant at a temperature of 25°. Remove the containers from the bath, shake, and remove the actuator and water, if any, from the valve stem. Place each container in an upright position, and determine the pressure in each container by placing a calibrated pressure gauge on the valve stem, holding firmly, and actuating the valve so that it is fully open.

The gauge is of a calibration approximating the expected pressure and is fitted with an adapter appropriate for the particular valve stem dimensions. Read the pressure directly from the gauge.

Minimum Fill

Topical aerosols meet the requirements for aerosols under *Minimum Fill* ⟨ 755 ⟩.

Leakage Test

Perform this test only on topical aerosols fitted with continuous valves.

Select 12 aerosol containers, and record the date and time to the nearest half hour. Weigh each container to the nearest mg, and record the weight, in mg, of each as W_1. Allow the containers to stand in an upright position at a temperature of 25.0 ± 2.0° for not less than 3 days, and again weigh each container, recording the weight, in mg, of each as W_2, and recording the date and time to the nearest half hour. Determine the time, *T*, in hours, during which the containers were under test. Calculate the leakage rate, in mg per year, of each container taken by the formula:

$$(365)(24/T)(W_1 - W_2).$$

Where plastic-coated glass aerosol containers are tested, dry the containers in a desiccator for 12 to 18 hours, and allow them to stand in a constant-humidity environment for 24 hours prior to determining the initial weight as indicated above. Conduct the test under the same constant-humidity conditions. Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Remove any residual contents by rinsing with suitable solvents, then rinse with a few portions of methanol. Retain as a unit the container, the valve, and all associated parts, and heat them at 100° for 5 minutes. Cool, weigh, record the weight as W_3, and determine the net fill weight ($W_1 - W_3$) for each container tested. [NOTE— If the average net fill weight has been determined previously, that value may be used in place of the value ($W_1 - W_3$) above.] The requirements are met if the average leakage rate per year for the 12 containers is not more than 3.5% of the net fill weight, and none of the containers leaks more than 5.0% of the net fill weight per year. If 1 container leaks more than 5.0% per year, and if none of the containers leaks more than 7.0% per year, determine the leakage rate of an additional 24 containers as directed herein. Not more than 2 of the 36 containers leak more than 5.0% of the net fill weight per year, and none of the 36 containers leaks more than 7.0% of the net fill weight per year. Where the net fill weight is less than 15 g and the label bears an expiration date, the requirements are met if the average leakage rate of the 12 containers is not more than 525 mg per year and none of the containers leaks more than 750 mg per year. If 1 container leaks more than 750 mg per year, but not more than 1.1 g per year, determine the leakage rate of an

additional 24 containers as directed herein. Not more than 2 of the 36 containers leak more than 750 mg per year, and none of the 36 containers leaks more than 1.1 g per year. This test is in addition to the customary in-line leak testing of each container.

Number of Discharges per Container

Perform this test only on topical aerosols fitted with dose-metering valves, at the same time as, and on the same containers used for, the test for *Delivered-Dose Uniformity*. Determine the number of discharges or deliveries by counting the number of priming discharges plus those used in determining the spray contents, and continue to fire until the label claim number of discharges. The requirements are met if all the containers or inhalers tested contain not less than the number of discharges stated on the label.

Delivered-Dose Uniformity

The test for *Delivered-Dose Uniformity* is required for topical aerosols fitted with dose-metering valves. For collection of the minimum dose, proceed as directed in the test for *Delivered-Dose Uniformity* under *Metered-Dose Inhalers and Dry Powder Inhalers,* as described below, except to modify the dose sampling apparatus so that it is capable of quantitatively capturing the delivered dose from the preparation being tested. Unless otherwise stated in the individual monograph, apply the acceptance criteria for *Metered-Dose Inhalers and Dry Powder Inhalers* as described below.

NASAL SPRAYS

The following test is applicable to nasal sprays, formulated as aqueous suspensions or solutions of drug, presented in multi-dose containers and fitted with dose-metering valves. In all cases, and for all tests, prepare and test the nasal spray as directed on the label and the instructions for use.

Delivered-Dose Uniformity

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered doses (minimum number of sprays per nostril as described on the label, or instructions for use) collected at the beginning of unit life (after priming as described on the label, or instructions for use) and at the label claim number of metered sprays, from each of 10 separate containers, must meet the following acceptance criteria: not more than 2 of the 20 doses are outside the range of 80% to 120% of label claim, and none are outside the range of 75% to 125% of label claim, while the mean for each of the beginning and end doses falls within the range of 85% to 115% of label claim. If 3–6 doses of the 20 doses collected are outside of 80% to 120% of the label claim, but none are outside of 75% to 125% of label claim, and the means for each of the beginning and end doses fall within 85% to 115% of label claim, select 20 additional containers for second-tier testing.

For second-tier testing, the requirements are met if not more than 6 of the 60 doses collected are outside the range of 80% to 120% of label claim, none are outside the range of 75% to 125% of label claim, and the means for each of the beginning and end doses fall within the range of 85% to 115% of label claim.

SAMPLING FOR DELIVERED-DOSE UNIFORMITY OF METERED-DOSE NASAL SPRAYS

General Sampling Procedure— To ensure reproducible in-vitro dose collection, it is recommended that a mechanical means of actuating the pump assembly be employed to deliver doses for collection. The mechanical actuation procedure should have adequate controls for the critical mechanical actuation parameters (e.g., actuation force, actuation speed, stroke length, rest periods, etc.). The test must be performed on units that have been primed according to the patient-use instructions. The test unit should be actuated in a vertical or near vertical, valve-up, position. The two doses collected at the beginning and end of the container life should be the dose immediately following priming and the dose corresponding to the last label claim number of doses from the container.

For suspension products, the delivered dose should be delivered into a suitable container (e.g., scintillation vial) in which quantitative transfer from the container under test can be accomplished. A validated analytical method is employed to determine the amount of drug in each delivered dose, and data are reported as a percent of label claim. For solution products, the delivered dose can be determined gravimetrically from the weight of the delivered dose, and the concentration and density of the fill solution of the product under test.

METERED-DOSE INHALERS AND DRY POWDER INHALERS

The following tests are applicable to metered-dose inhalers that are formulated as suspensions or solutions of active drug in propellants and dry powder inhalers presented as single or multidose units. The following test methods are specific to the aforementioned inhalers and may require modification when testing alternative inhalation technologies (for example, breath-actuated metered-dose inhalers, or dose-metering nebulizers). However, Pharmacopeial requirements for all dose-metering inhalation dosage forms require determination of the delivered dose and *Aerodynamic Size Distribution.* In all cases, and for all tests, prepare and test the inhaler as directed on the label and the instructions for use. When these directions are not provided by the product manufacturer, follow the precise dose discharge directions included in the tests below.

Delivered-Dose Uniformity

The test for *Delivered-Dose Uniformity* is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing drug formulation (e.g., solution, suspension, or powder) either in reservoirs or in premetered dosage units, and for drug formulations

packaged in reservoirs or in premetered dosage units where these containers are labeled for use with a named inhalation device. (For inhalations packaged in premetered dosage units, see also *Uniformity of Dosage Units* ⟨ 905 ⟩ .) Note that the target-delivered dose is the expected mean drug content for a large number of delivered doses collected from many inhalers of the chosen product. In many cases, its value may depend upon the manner in which the test for delivered dose is performed. For metered-dose inhalers, the target-delivered dose is specified by the label claim, unless otherwise specified in the individual monograph. For dry powder inhalers, where the label claim is usually the packaged or metered-dose of drug, the target-delivered dose is specified in the individual monograph and is usually less than the label claim. Its value reflects the expected mean drug content for a large number of delivered doses collected from the product, using the method specified in the monograph.

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered dose from each of 10 separate containers is determined in accordance with the procedure described below.

Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if not less than 9 of the 10 doses are between 75% and 125% of the specified target-delivered dose and none is outside the range of 65% to 135% of the specified target-delivered dose. If the contents of not more than 3 doses are outside the range of 75% to 125% of the specified target-delivered dose, but within the range of 65% to 135% of the specified target-delivered dose, select 20 additional containers, and follow the prescribed procedure for analyzing 1 minimum dose from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of 75% to 125% of the specified target-delivered dose, and none is outside the range of 65% to 135% of the specified target-delivered dose.

SAMPLING THE DELIVERED DOSE FROM METERED-DOSE INHALERS

To determine the content of active ingredient in the discharged spray from a metered-dose inhaler, use the sampling apparatus described below, using a flow rate of 28.3 L of air per minute (±5%), unless otherwise stated in the individual monograph.

Apparatus A— The apparatus (see *Figure 1*)

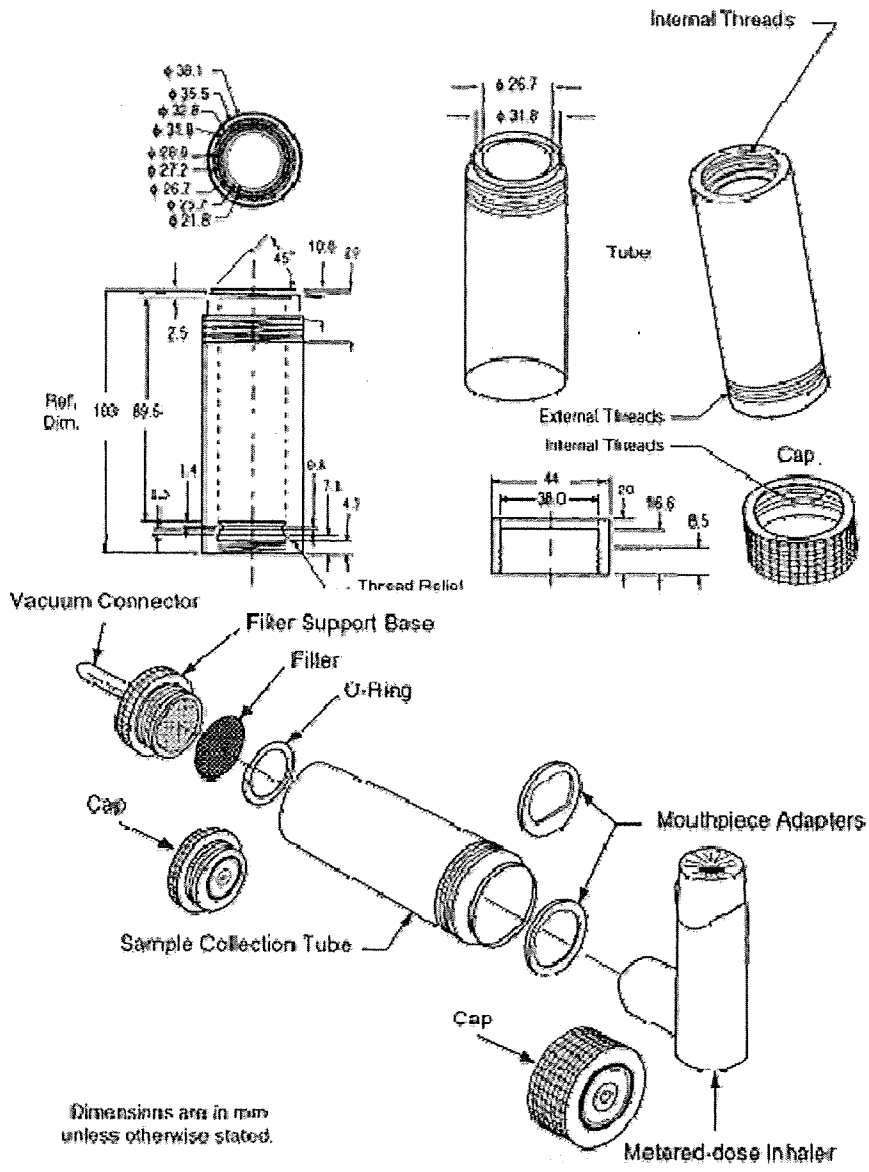

Fig. 1. Sampling apparatus for pressurized metered-dose inhalers.

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 opening of the inhaler mouthpiece is flush with the front face or 2.5-mm indented shoulder in the sample collection tube, as appropriate. The vacuum connector is connected to a system comprising a vacuum source, flow regulator, and flowmeter. The source should be capable of pulling air through the complete assembly, including the filter and the inhaler to be tested, at the desired flow rate. When testing metered-dose inhalers, air should be drawn continuously through the system to avoid loss of drug into the atmosphere. The filter support base is designed to accommodate 25-mm diameter filter disks. At the airflow being used, the sample collection tube and the filter disk must be capable of quantitatively

collecting the *Delivered Dose.* The filter disk and other materials used in the construction of the apparatus must be compatible with the drug and the solvents that are used to extract the drug 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 device passes through the inhaler.

Procedure— Prepare the inhaler for use according to the label instructions. Unless otherwise specified in the individual monograph, with the vacuum pump running, ensuring an airflow rate through the inhaler of 28.3 L of air per minute (±5%), discharge the minimum recommended dose into the apparatus through the mouthpiece adapter by depressing the valve for a duration sufficient to ensure that the dose has been completely discharged. Detach the inhaler from *Apparatus A,* and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent.

SAMPLING THE DELIVERED DOSE FROM DRY POWDER INHALERS

To determine the content of active ingredient emitted from the mouthpiece of a dry powder inhaler, use *Apparatus B* (see *Figure 2*).

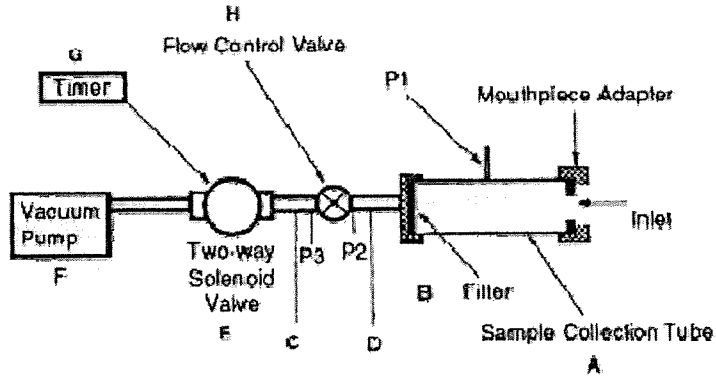

Fig. 2. Apparatus B: Sampling apparatus for dry powder inhalers. (See *Table 1* for component specifications.)

Table 1. Component Specifications for Apparatus B (see *Fig. 2*)

Code	Item	Description	Dimensions
A	Sample collection tube[a]	See *Fig. 2*	34.85-mm ID × 12-cm length
B	Filter[b]	See *Fig. 2*	47-mm glass fiber filter
C	Connector	(e.g., short metal coupling with low diameter	≥8-mm ID

		branch to P3)	
D	Vacuum tubing	(e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm)	a length of suitable tubing ≥8 mm ID with an internal volume of 25 ± 5 mL.
E	Two-way solenoid valve[c]	See *Fig. 2*	2-way, 2-port solenoid valve having an ID ≥8 mm and an opening response time of ≤100 milliseconds.
F	Vacuum pump[d]	See *Fig. 2*	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide (≥10-mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
G	Timer[e]	See *Fig. 2*	The timer switches current directly to the solenoid valve for the required duration.
P1	pressure tap	See *Fig. 2*	2.2-mm ID, 3.1-mm OD flush with the internal surface of the sample collection tube, centered and burr free, 59 mm from its inlet. The pressure taps P1, P2, and P3 must not be open to the atmosphere during dose collection.
P1, P2, P3	pressure measurements[f]		
H	Flow-control valve[g]	See *Fig. 2*	Adjustable regulating valve with maximum $C_V \geq 1$[h].

[a] An example being a Millipore product number XX40 047 00 (Millipore Corporation, 80, Ashby Road, Bedford, MA 01732), modified so that the exit tube

has an ID ≥ 8-mm, fitted with Gelman product number 61631.

[b] A/E (Gelman Sciences Inc., 600 South Wagner Road, Ann Arbor, MI 48106) or equivalent.

[c] ASCO product number 8030G13, Automatic Switch Company, 60 Hanover Road, Florham Park, NJ 07932.

[d] Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.

[e] Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901, South 12th Street, Watertown, WI 53094) or equivalent.

[f] An example being a PDM 210 pressure meter (Air-Neotronics Ltd., Neotronics Technology plc, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK), or equivalent.

[g] Parker Hannifin type 8FV12LNSS (Parker Hannifin plc., Riverside Road, Barnstable, Devon EX31 1NP, UK) or equivalent.

[h] Flow Coefficient, as defined by ISA S75.02 "Control valve capacity test procedure" in *Standards and Recommended Practices for Instrumentation and Control*, 10th ed., Vol. 2, 1989. Published by Instrument Society of America, 67 Alexander Drive, P.O. Box 1227, Research Triangle Park, NC 27709, U.S.A.

This apparatus is capable of sampling the emitted doses at a variety of airflow rates.

Apparatus B— The apparatus is similar to that described in *Figure 1* for testing metered-dose inhalers. In this case, however, the filter and collection tube have a larger internal diameter to accommodate 47-mm diameter filter disks. This feature enables dosage collection at higher airflow rates—up to 100 L of air per minute—when necessary. A mouthpiece adapter ensures an airtight seal between the collection tube and the mouthpiece of the dry powder inhaler being tested. The mouthpiece adapter must ensure that the tip of the inhaler mouthpiece is flush with the open end of the sample collection tube. Tubing connectors, if they are used, should have an internal diameter greater than or equal to 8 mm to preclude their own internal diameters from creating significant airflow resistance. A vacuum pump with excess capacity must be selected in order to draw air, at the designated volumetric flow rate, through both the sampling apparatus and the inhaler simultaneously. A timer-controlled, low resistance, solenoid-operated, two-way valve is interposed between the vacuum pump and the flow-control valve to control the duration of flow. This type of valve enables 4.0 L of air (±5%) to be withdrawn from the mouthpiece of the inhaler at the designated flow rate. Flow control is achieved by ensuring that critical (sonic) flow occurs in the flow-control valve (absolute pressure ratio P3/P2 ≤ 0.5 under conditions of steady-state flow).

Procedure— Operate the apparatus at an airflow rate that produces a pressure drop of 4 kPa (40.8 cm H_2O) over the inhaler to be tested and at a duration consistent with the withdrawal of 4 L of air from the mouthpiece of the inhaler. [NOTE— If the flow rate and duration are defined otherwise in the monograph, adjust the system to within 5% of those values.] Determine the test flow rate using *Apparatus B* as follows. Insert an inhaler into the mouthpiece adapter to ensure an airtight seal. In cases where the drug packaging modifies the inhaler's resistance to airflow, use a loaded, drug-free inhaler (with previously emptied packaging). In other cases, use an unloaded (drug free) inhaler. Connect one port of a differential pressure transducer to the pressure tap, P1, and leave the other open to the atmosphere. Switch on the pump, and open the two-way solenoid valve. Adjust the flow-control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H_2O). Ensure that critical (sonic) flow occurs in the flow-control valve by determining the individual values for absolute pressure, P2 and P3, so that their ratio P3/P2 is less than or equal to 0.5. If this criterion cannot be achieved, it is likely that the vacuum pump is worn or of insufficient capacity. Critical (sonic) flow conditions in the flow-control valve are required in order to ensure that the volumetric airflow drawn from the mouthpiece is unaffected by pump fluctuations and changes in airflow resistance of the inhaler. Remove the inhaler from the mouthpiece adapter and without disturbing the flow-control valve, measure the airflow rate drawn from the mouthpiece, Q_{out}, by connecting a flowmeter to the mouthpiece adaptor in an airtight fashion. Use a flowmeter calibrated for the volumetric flow leaving the meter in an airtight fashion to directly determine Q_{out} or, if

such a meter is unobtainable, calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For example, 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. If the flow rate is greater than 100 L of air per minute, adjust the flow-control valve until Q_{out} equals 100 L per minute; otherwise, record the value of Q_{out} , and leave the flow-control valve undisturbed. Define the test flow duration, $T = 240/ Q_{out}$, in seconds, so that a volume of 4.0 L of air (±5%) is withdrawn from the inhaler at the test flow rate Q_{out} ,, and adjust the timer controlling the operation of the two-way solenoid valve accordingly. Prime or load the inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the solenoid valve closed, insert the inhaler mouthpiece horizontally into the mouthpiece adapter. Discharge the powder into the sampling apparatus by activating the timer controlling the solenoid valve and withdrawing 4.0 L of air from the inhaler at the previously defined airflow rate. If the labeled instructions so direct, repeat the operation so as to simulate the use of the inhaler by the patient (e.g., inhale two or three times, if necessary, to empty the capsule). Repeat the whole operation $n - 1$ times beginning with the text, "Prime or load the inhaler with powder," where n is the number of times defined in the labeling as the minimum recommended dose. Detach the dry powder inhaler from the sampling apparatus, and disconnect the vacuum tubing, D. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Where specified in individual monographs, perform this test under conditions of controlled temperature and humidity.

Delivered-Dose Uniformity over the Entire Contents

The test for *Delivered-Dose Uniformity over the Entire Contents* is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing multiple doses of drug formulation (e.g., solution, suspension, or dry powder) either in reservoirs or in premetered dosage units (e.g., blisters), and for drug formulations packaged in reservoirs or in multiple-dose assemblies of premetered dosage units that have a predetermined dose sequence, where these multiple-dose assemblies are labeled for use with a named inhalation device. The test for *Delivered-Dose Uniformity over the Entire Contents* also ensures that multidose products supply the total number of discharges stated on the label. Unless otherwise directed in the individual monograph, the drug content of at least 9 of the 10 doses collected from one inhaler, in accordance with the procedure below, are between 75% and 125% of the target-delivered dose, and none is outside the range of 65% to 135% of the target-delivered dose. If the contents of not more than 3 doses are outside the range of 75% to 125%, but within the range of 65% to 135% of the target-delivered dose, select 2 additional inhalers, and follow the prescribed procedure for

analyzing 10 doses from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of 75% to 125% of the target-delivered dose, and none is outside the range of 65% to 135% of the target-delivered dose.

METERED-DOSE INHALERS

Apparatus— Use *Apparatus A* as directed in *Sampling the Delivered-Dose from Metered-Dose Inhalers* under *Delivered-Dose Uniformity* at a flow rate of 28.3 L of air per minute (±5%).

Procedure— A single dose is defined as the number of sprays specified in the product labeling as the minimum recommended dose. Select a single metered-dose inhaler, and follow the labeled instructions for priming, shaking, cleaning, and firing the inhaler throughout. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and fire one minimum recommended dose to waste. Wait for 5 seconds, and collect the next dose. Detach the inhaler from *Apparatus A*, and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Collect two more doses, allowing at least 5 seconds between doses. Discharge the device to waste, waiting for not less than 5 seconds between actuations (unless otherwise specified in the individual monograph), until (n/2) + 1 minimum recommended doses remain, in which n is the number of minimum recommended doses on the label. Collect four more doses, allowing at least 5 seconds between doses, unless otherwise specified in the individual monograph. Discharge the device to waste, as before, until three doses remain. Collect the final three doses, allowing at least 5 seconds between doses. Note that the rate of discharges to waste should not be such to cause excessive canister cooling.

DRY POWDER INHALERS

Apparatus— Use *Apparatus B* as directed in *Sampling the Delivered Dose from Dry Powder Inhalers* under *Delivered-Dose Uniformity* at the appropriate airflow rate for testing.

Procedure— Proceed as directed for *Procedure* in *Sampling the Delivered Dose from Dry Powder Inhalers* under *Delivered-Dose Uniformity.* A single dose is defined as the number of actuations stated in the product labeling as the minimum recommended dose. Select a single inhaler and follow the labeled instructions for loading with powder, discharging and cleaning throughout. Collect a total of 10 doses—three doses at the beginning, four in the middle [(n/2) − 1 to (n/2) + 2, where n is the number of minimum recommended doses on the label], and three at the end—of the labeled contents following the labeled instructions. Prior to collecting each of the doses to be analyzed, clean the inhaler as directed in the labeling.

Particle Size