GLOBAL DOCUMENT

DISSOLUTION

This test is provided to determine compliance with the dissolution requirements for dosage forms administered orally. In this General Chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified.

APPARATUS

Apparatus 1 (Basket Apparatus) —The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material[1]; a motor; a drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits maintaining the temperature of the Dissolution Medium inside the vessel at 37.0 ± 0.5º during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element, which keeps the Dissolution Medium in constant smooth motion. Apparatus that permits observation of the dosage unit and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and a capacity of 1 liter. Its height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm. Its sides may be flanged at the top. A fitted cover

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

may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or other inert material, to the specifications shown in Figure 1. A basket having a gold coating of about 2.5 µm thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

Apparatus 2 (Paddle Apparatus) —Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel, at any point, and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 2a. Other validated sinker devices may be used.

Apparatus 3 (Reciprocating Cylinder)—

[NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA]

The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material) and screens that are made of suitable nonsorbing and nonreactive material and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature of the Dissolution Medium inside the vessel at 37.0 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate, within ±5%. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. An apparatus that permits observation of the dosage form and reciprocating cylinders

is preferable. The vessels are provided with an evaporation cap that remains in place for the duration of the test. The components conform to the dimensions shown in Figure 3 unless otherwise specified.

Apparatus 4 (Flow-Through Cell) —The assembly consists of a reservoir and a pump for the Dissolution Medium; a flow-through cell; a water bath that maintains the Dissolution Medium at 37.0 ± 0.5°. Use the specified cell size.

The pump forces the Dissolution Medium upwards through the flow-through cell. The pump has a delivery range between 240 and 960 ml per hour, with standard flow rates of 4, 8, and 16 ml per minute. It must deliver a constant flow (± 5 per cent of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute. A pump without pulsation may also be used. Dissolution test procedures using the flow-through cell must be characterized with respect to rate and pulsation.

The flow-through cell (see Figures 4 and 5), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a dosage form holder (see Figures 4 and 5) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature in the cell is maintained at 37.0 ± 0.5°.

The apparatus uses a clamp mechanism of two O-rings to assemble the cell. The pump is separated from the dissolution unit in order to shield the latter against any

vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections.

Apparatus Suitability—The determination of suitability of a test assembly to perform dissolution testing must include conformance to the dimensions and tolerances of the apparatus as given above. In addition, critical test parameters that have to be monitored periodically during use include volume and temperature of the Dissolution Medium, rotation speed (Apparatus1 and Apparatus 2), dip rate (Apparatus 3), and flow rate of medium (Apparatus 4).

Determine the acceptable performance of the dissolution test assembly periodically.

PROCEDURE

APPARATUS 1 OR 2

IMMEDIATE-RELEASE DOSAGE FORMS

Procedure—Place the stated volume of the Dissolution Medium (±1%) in the vessel of the specified apparatus, assemble the apparatus, equilibrate the Dissolution Medium to 37.0 ± 0.5º, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw an aliquot from a zone midway between the surface of the Dissolution Medium and the top of the rotating basket or blade, not less than 1 cm from

the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37º or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the medium under test at suitable times.] Perform the analysis using a suitable assay method. [3] Repeat the test with additional dosage units.

If automated equipment is used for sampling or the apparatus is modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this General Chapter is necessary.

Dissolution Medium—A suitable dissolution medium is used. The volume specified refers to measurements made between 20° and 25°. If the Dissolution Medium is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.[4]]

Time—Aliquots are to be withdrawn only at the stated times, within a tolerance of ±2%. Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met.

EXTENDED-RELEASE DOSAGE FORMS

Procedure—Proceed as described for Immediate-Release Dosage Forms.

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[3] The sample aliquots are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41º, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

Dissolution Medium—Proceed as directed under Immediate-Release Dosage Forms.

Time—The test-time points, generally three, are expressed in hours.

DELAYED-RELEASE DOSAGE FORMS

[NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA]

Procedure—Use Method A or Method B

Method A

Acid stage—Place 750 ml of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium in the vessel to equilibrate to a temperature of 37.0 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer stage*.

Perform an analysis of the aliquot using a suitable assay method.

Buffer stage—[NOTE—Complete the operations of adding the buffer solution, and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified, add to the fluid in the vessel 250 ml of 0.20 M tribasic sodium phosphate that has been equilibrated to 37.0 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.80 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method.

Method B

Acid Stage—Place 1000 ml of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium in the vessel to equilibrate to a temperature of 37.0 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the

specified rate. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer stage*.

Perform an analysis of the aliquot using a suitable assay method.

Buffer stage—[NOTE—For this stage of the procedure, use buffer solution that previously has been equilibrated to a temperature of 37.0 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 ml of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.80 ± 0.05. [NOTE—This may be accomplished also by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer solution and transferring the dosage unit to the vessel containing the buffer solution.] Continue to operate the apparatus for 45 minutes, or for the specified time. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method.

Time—All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

APPARATUS 3

[NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA]

IMMEDIATE-RELEASE DOSAGE FORMS

Procedure— A dissolution test can be conducted either in one vessel or in a set of subsequent vessels by moving the reciprocating cylinder from vessel to vessel. Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the

apparatus, equilibrate the *Dissolution Medium* to 37.0 ± 0.5°, and remove the thermometer. Place 1 dosage unit in each of the reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage unit, and immediately operate the apparatus as specified. When the test is conducted in one vessel at each of the times stated, raise the reciprocating cylinders and withdraw an aliquot of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. When the dissolution test is conducted in multiple vessels, at the stated times the reciprocating cylinder moves to the subsequent vessel and aliquots of the solution under test are withdrawn from the vessel immediately after. Perform the analysis as directed. Repeat the test with additional dosage units.

When the test is conducted in one vessel, replace the aliquot withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered with the evaporation cap for the duration of the test, and verify the temperature of the medium under test at suitable times.

Dissolution Medium—Proceed as directed under Immediate-Release Dosage Forms under Apparatus 1 or 2.

Time — Proceed as directed under Immediate-Release Dosage Forms under Apparatus 1 or 2.

EXTENDED-RELEASE DOSAGE FORMS

Procedure— Proceed as described for Immediate-Release Dosage Forms under Apparatus 3.

Dissolution Medium— Proceed as described for Immediate-Release Dosage Forms under Apparatus 1 or 2.

Time— Proceed as described for Extended-Release Dosage Forms under Apparatus 1 or 2.

DELAYED-RELEASE DOSAGE FORMS

Procedure— Proceed as described for Delayed-Release Dosage Forms Method B under Apparatus 1 or 2 using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time — Proceed as directed for Delayed-Release Dosage Forms under Apparatus 1 or 2.

APPARATUS 4

IMMEDIATE-RELEASE DOSAGE FORMS

Procedure— Place the glass beads into the cell specified. Place 1 dosage unit on top of the beads or, if specified, in a dosage form holder (see Figure 4 and Figure 5). Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37.0 ± 0.5° through the bottom of the cell to obtain the flow rate specified and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed. Repeat the test with additional dosage units.

Dissolution Medium— Proceed as directed under Immediate-Release Dosage Forms under Apparatus 1 or 2.

Time — Proceed as directed under Immediate-Release Dosage Forms under Apparatus 1 or 2.

EXTENDED-RELEASE DOSAGE FORMS

Procedure— Proceed as described for Immediate-Release Dosage Forms under Apparatus 4.

Dissolution Medium—Proceed as described for Immediate-Release Dosage Forms under Apparatus 1 or 2.

Time—Proceed as described for Extended-Release Dosage Forms under Apparatus 1 or 2.

DELAYED-RELEASE DOSAGE FORMS

[NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA]

Procedure— Proceed as described for Immediate-Release Dosage Forms under Apparatus 4

Dissolution Media – Proceed using the specified media as described for Delayed-Release Dosage Forms under Apparatus 1 or 2.

Time — Proceed as directed for Delayed-Release Dosage Forms under Apparatus 1 or 2.

INTERPRETATION

IMMEDIATE-RELEASE DOSAGE FORMS

Unless otherwise specified, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to the accompanying

Acceptance Table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the specified amount of dissolved active ingredient, expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in the Acceptance Table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number of dosage units Tested	Acceptance Criteria
S_1	6	No individual value is less than Q + 5%.
S_2	6	Average value of the 12 dosage units ($S_1 + S_2$) is equal to or greater than Q, and no value is less than Q – 15%.
S_3	12	Average value of the 24 dosage units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 values are less than Q – 15%, and no value is less than Q – 25%.

EXTENDED-RELEASE DOSAGE FORMS

Unless otherwise specified, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the

amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified, the acceptance criteria apply individually to each range.

Acceptance Table 2

Level	Number of dosage units Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 dosage units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; no value is more than 10% of labeled content outside each of the stated ranges; and no value is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 dosage units (L_1 + L_2 + L_3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 values

		are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 values are more than 10% of labeled content below the stated amount at the final test time; and no value is more than 20% of labeled content outside each of the stated ranges and more than 20% of labeled content below the stated amount at the final test time.

DELAYED-RELEASE DOSAGE FORMS [NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA]

Acid stage — Unless otherwise specified, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to Acceptance Table 3. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 3

Level	Number of dosage units Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	The average value of the 12 dosage units (A_1 + A_2) is not more than 10% dissolved, and no value is greater than 25% dissolved.
A_3	12	The average value of the 24 dosage units (A_1 + A_2 + A_3) is not more than 10% dissolved, and no value is greater than 25% dissolved.

Buffer stage — Unless otherwise specified, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to Acceptance Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Acceptance Table 4 is 75% dissolved unless otherwise specified. The quantity, Q, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content. The 5% and 15% values in Acceptance Table 4 are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number of dosage units Tested	Criteria
B_1	6	No individual value is less than Q + 5%.
B_2	6	The average value of the 12 dosage units ($B_1 + B_2$) is equal to or greater than Q, and no value is less than Q - 15%.
B_3	12	The average value of the 24 dosage units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 values are less than Q - 15%, and no value is less than Q - 25%.

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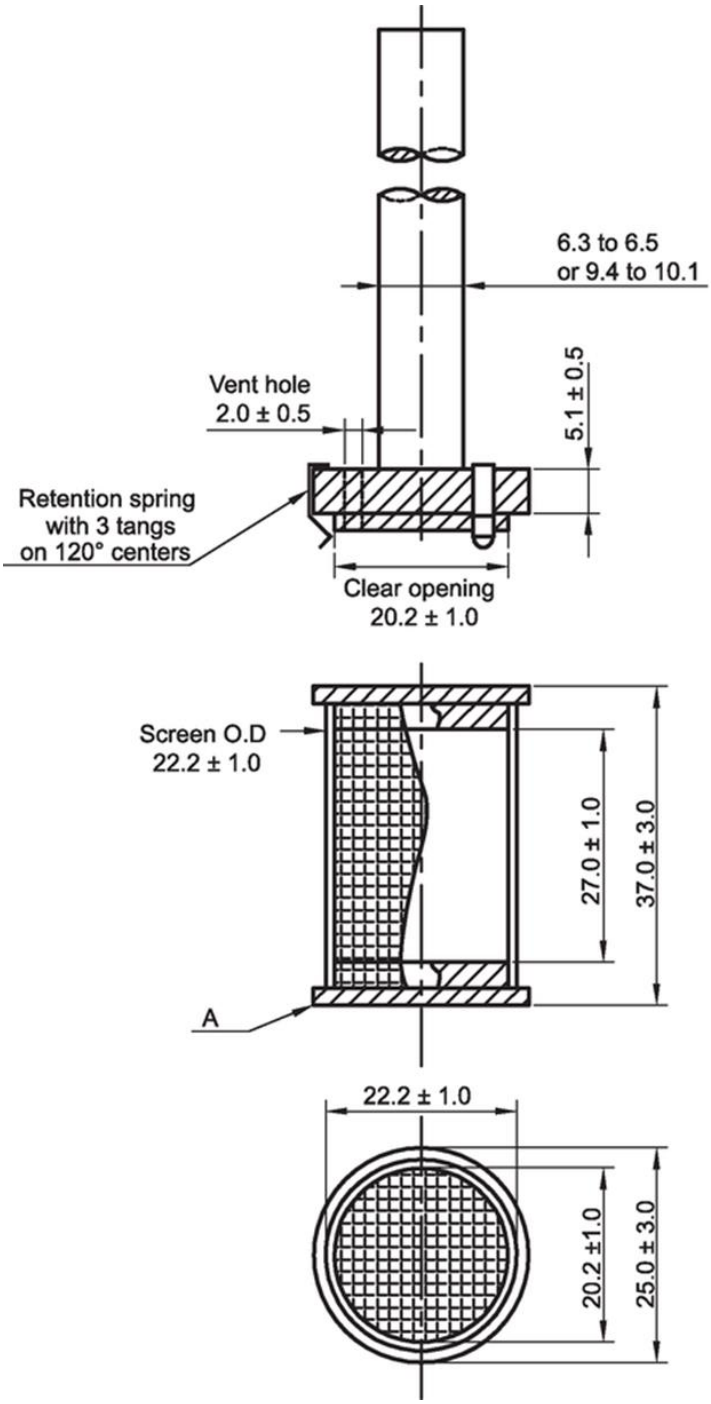

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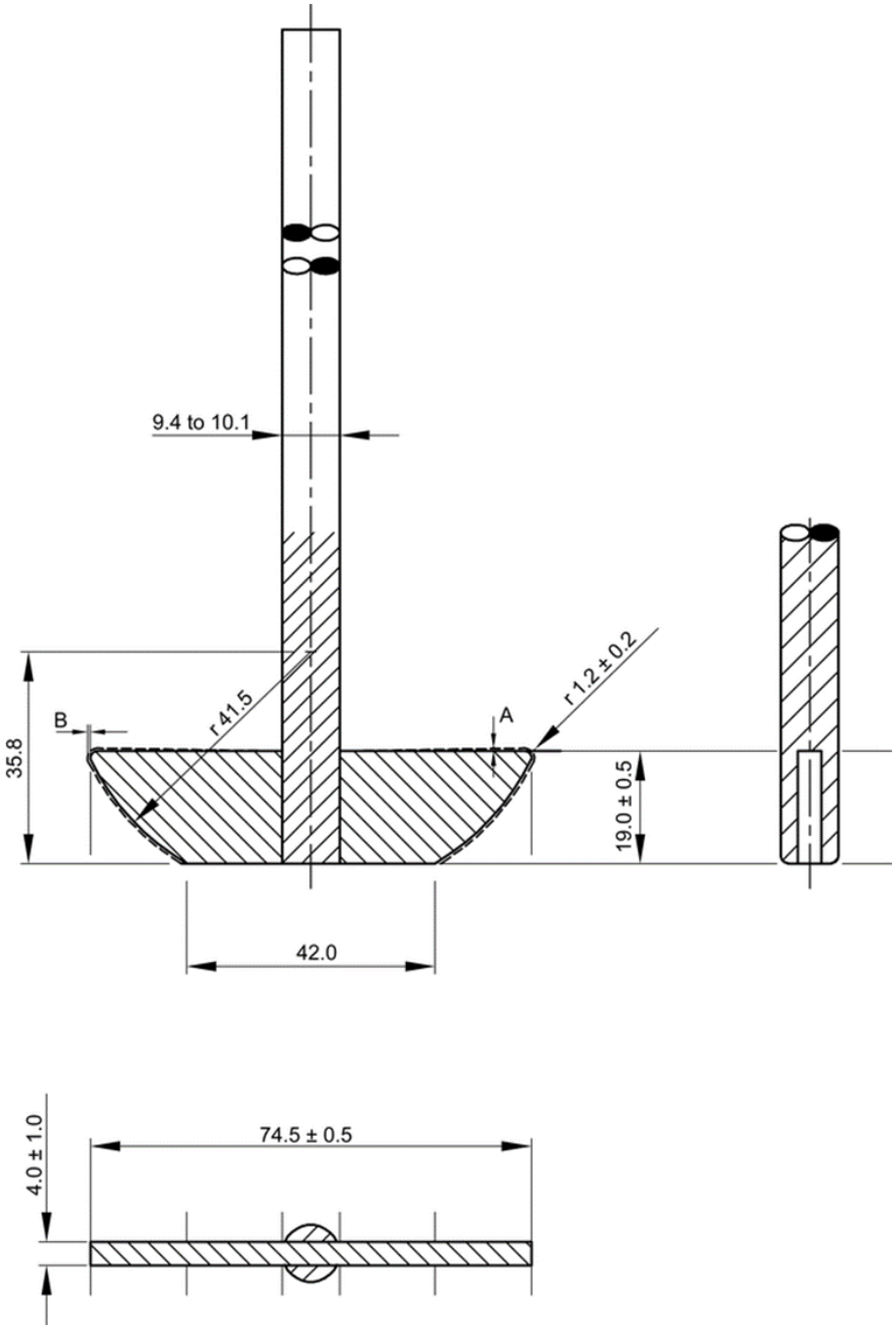
1) Screen with welded seam: 0.22-0.31 mm wire diameter with wire opening of 0.36-0.44 mm. After welding the screen may be slightly altered.

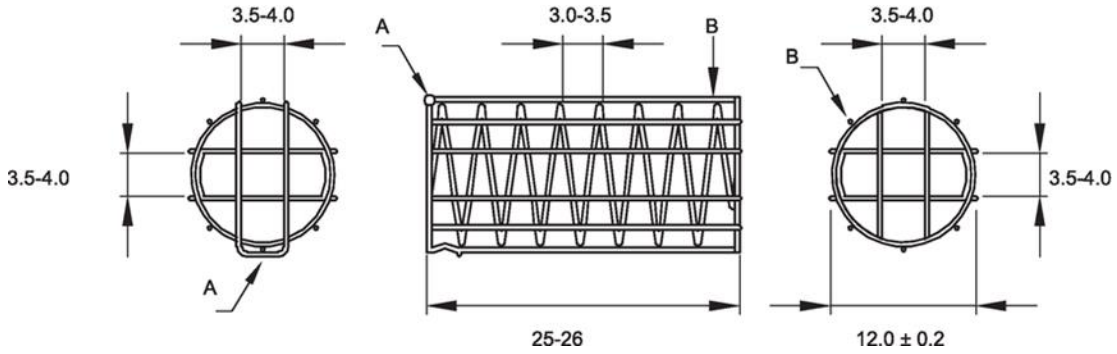
2) Maximum allowable runout at A is 1.0 mm when the part is rotated on center line axis with basket mounted.

299 Figure 1. – *Apparatus 1, Basket stirring element*
300 *Dimensions in millimetres*



A and B dimensions do not vary more than 0.5 mm when part is rotated on center line axis.
Tolerances are ± 1.0 mm unless otherwise stated.

Figure 2. – *Apparatus 2, Paddle stirring element*
Dimensions in millimetres



A: acid-resistant wire clasp B: acid-resistant wire support

Figure 2a. – *Alternative sinker*
Dimensions in millimetres

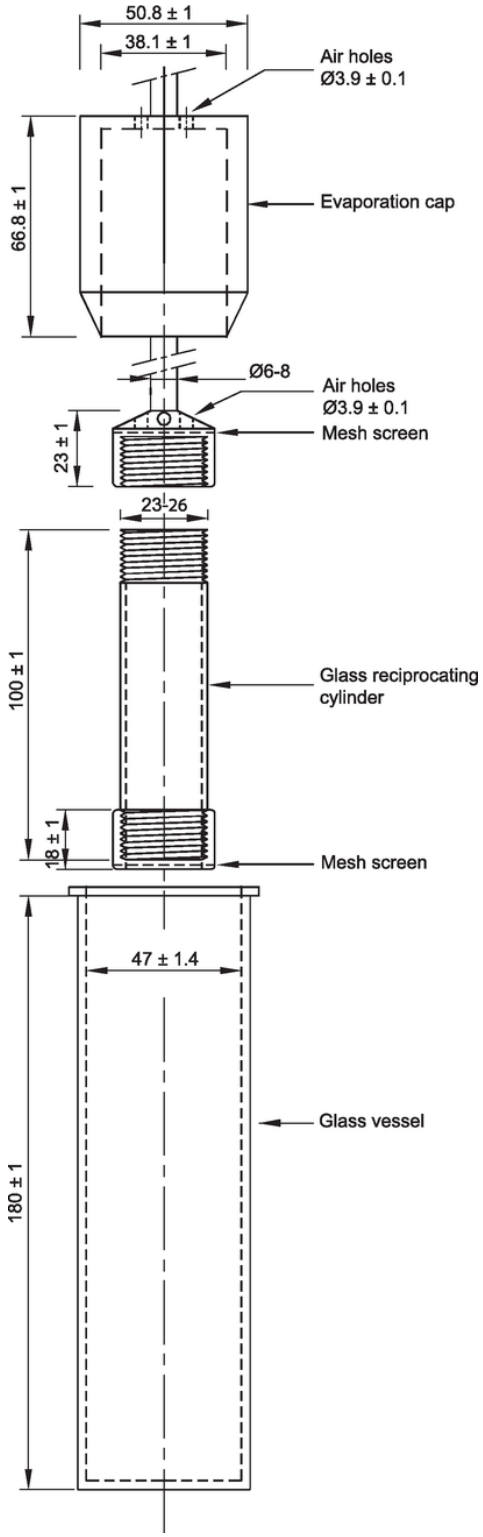


Figure 3 – *Apparatus 3, glass vessel and reciprocating cylinder*
Dimensions in millimetres

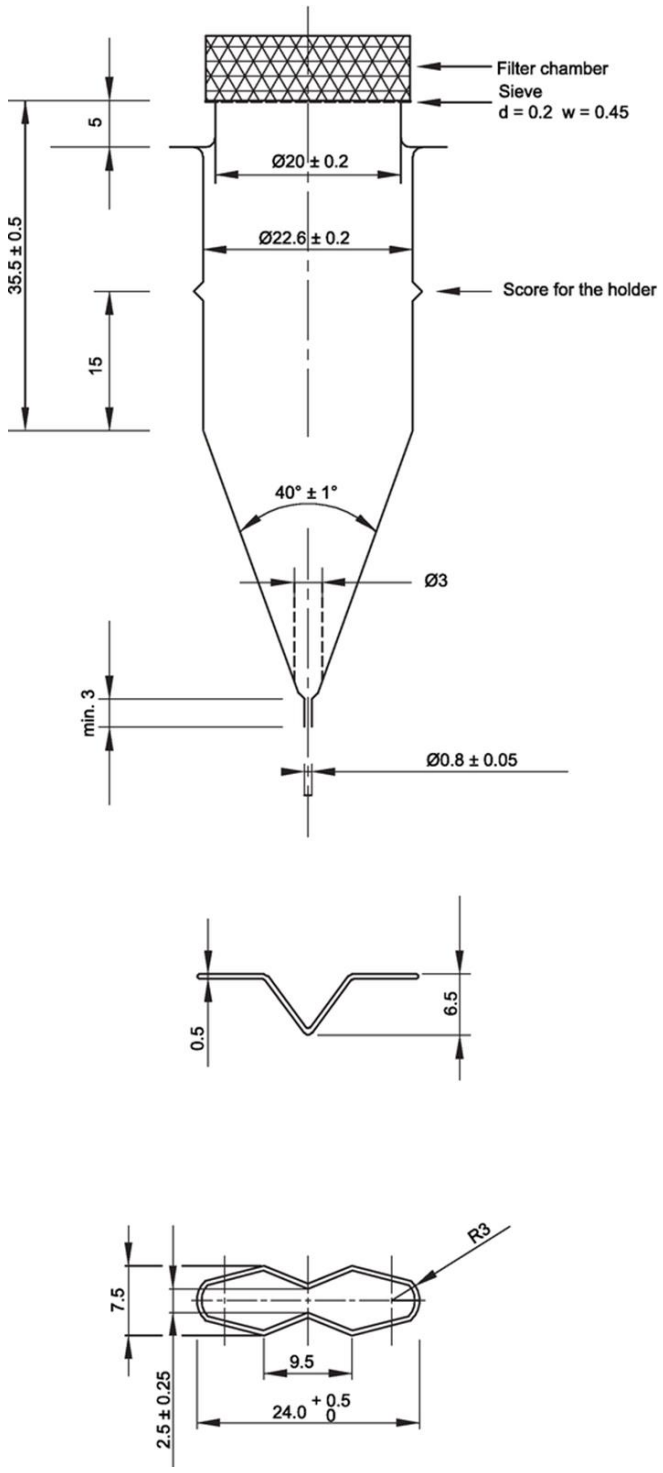


Figure 4. – *Apparatus 4, large cell for tablets and capsules (top), dosage form holder for the large cell (bottom)*
Dimensions in millimetres

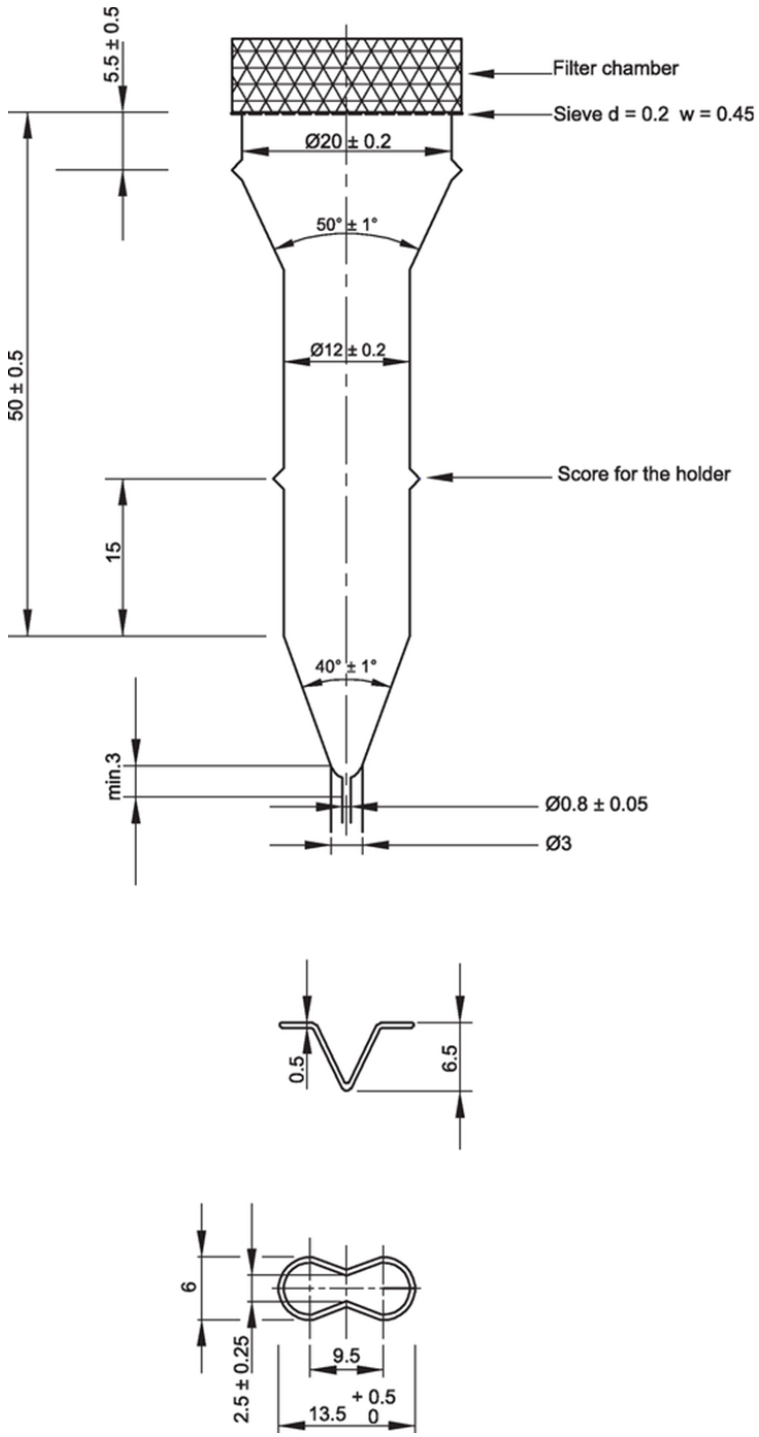


Figure 5. – *Apparatus 4, small cell for tablets and capsules (top), dosage form holder for the small cell (bottom)*
Dimensions in millimetres