water maintained at 36-37 °C, unless otherwise prescribed. The apparatuses may also be placed together in a vessel with a capacity of at least 12 L. The beaker is fitted with a slow stirrer and a device that will hold the cylinders vertically not less than 90 mm below the surface of the water and allow them to be inverted without emerging from the water.

PROCEDURE FOR SOLID RECTAL AND VAGINAL DOSAGE FORMS OTHER THAN VAGINAL TABLETS

Test 3 dosage units. Place each one on the lower disc of a metal device, place the latter in the cylindrical sleeve and secure. Invert the apparatuses every 10 min. At the end of the specified time, examine the samples. The requirements of the test are met if all the samples have disintegrated.

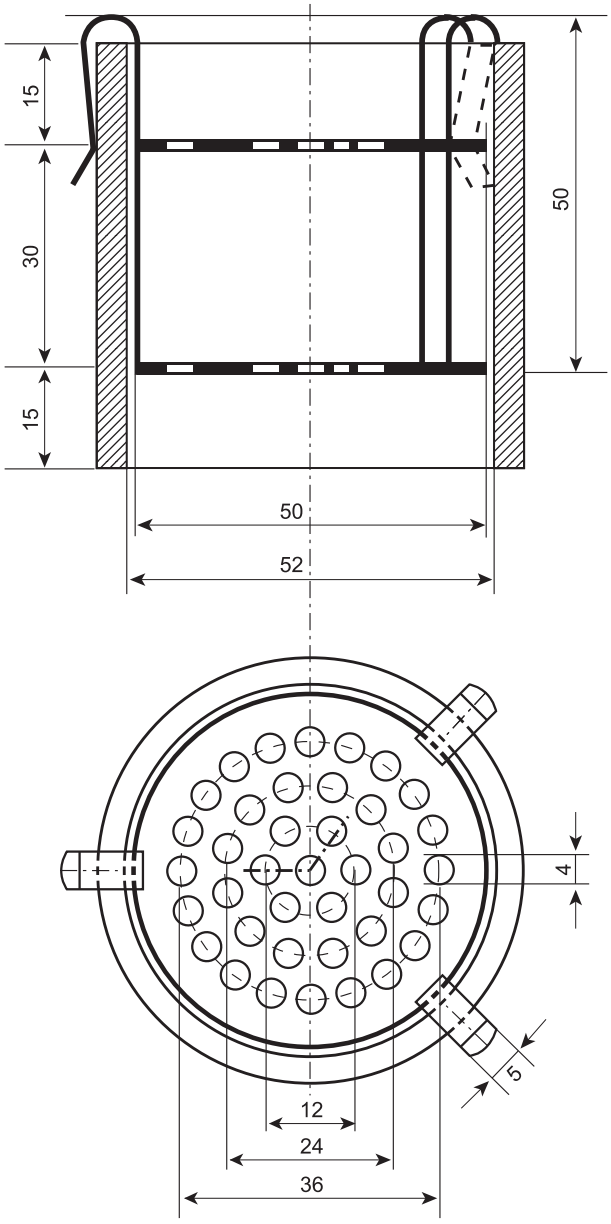
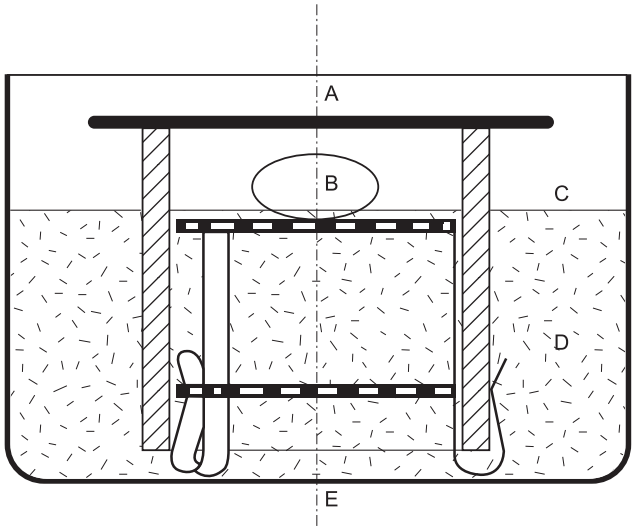


Figure 2.9.2.-1. – *Disintegration apparatus for solid rectal and vaginal dosage forms*
Dimensions in millimetres

PROCEDURE FOR VAGINAL TABLETS

Use the apparatus described above, turning it upside down so it rests on the spring clips (see Figure 2.9.2.-2). Place it in a beaker of suitable diameter containing water maintained at 36-37 °C with the level just below the upper perforated disc. Using a pipette, adjust the level with water until a uniform film covers the holes in the disc. Test 3 vaginal tablets. Place each one on the upper disc of an apparatus and cover the latter with a glass plate to maintain appropriate humidity. At the end of the specified time, examine the samples. The requirements of the test are met if all the samples have disintegrated.



A. glass plate
B. vaginal tablet
C. water surface
D. water
E. beaker

Figure 2.9.2.-2. – *Disintegration apparatus for vaginal tablets*

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2.9.3. DISSOLUTION TEST FOR SOLID DOSAGE FORMS[(2)]

This test is provided to determine compliance with the dissolution requirements for solid dosage forms administered orally. In this 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[(3)]; a motor; a drive shaft; and a cylindrical basket (stirring element). 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 inside the vessel at 37 ± 0.5 °C during the test and keeping the dissolution medium in constant, smooth motion. 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. 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 L. Its height is 160-210 mm and its inside diameter is 98-106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation[(4)]. 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

(2) This chapter has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.
(3) The materials must not sorb, react, or interfere with the preparation to be tested.
(4) If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of samples.

speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate, within ± 4 per cent.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 2.9.3.-1.

A basket having a gold coating of about 2.5 µm (0.0001 inch) 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.

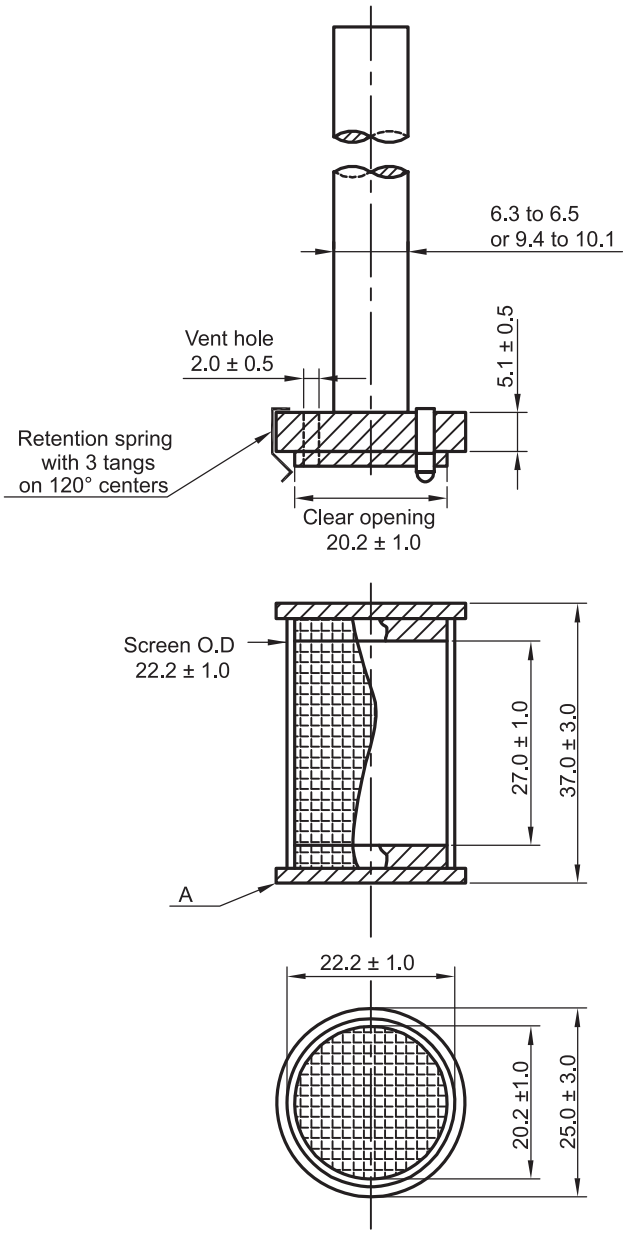
Apparatus 2 (Paddle apparatus). Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel, at any point, and rotates smoothly without significant 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 2.9.3.-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 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 non-reactive 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 2.9.3.-3. Other validated sinker devices may be used.

Apparatus 3 (Reciprocating cylinder). 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; 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 holding the temperature at 37 ± 0.5 °C 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 per cent. An apparatus that permits observation of the dosage unit 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 2.9.3.-4 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 ± 0.5 °C. 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 mL/h and 960 mL/h, with standard flow rates of 4 mL/min, 8 mL/min, and 16 mL/min. 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/min. A pump without pulsation may also be used. Dissolution test procedures using the flow-through cell must be characterised with respect to rate and any pulsation.

The flow-through cell (see Figures 2.9.3.-5 and 2.9.3.-6) of transparent and inert material is mounted vertically, with a filter system that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 mm and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1 mm diameter, with 1 bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see Figures 2.9.3.-5 and 2.9.3.-6) is available for positioning of special dosage forms. The cell is immersed in a water-bath, and the temperature is maintained at 37 ± 0.5 °C.

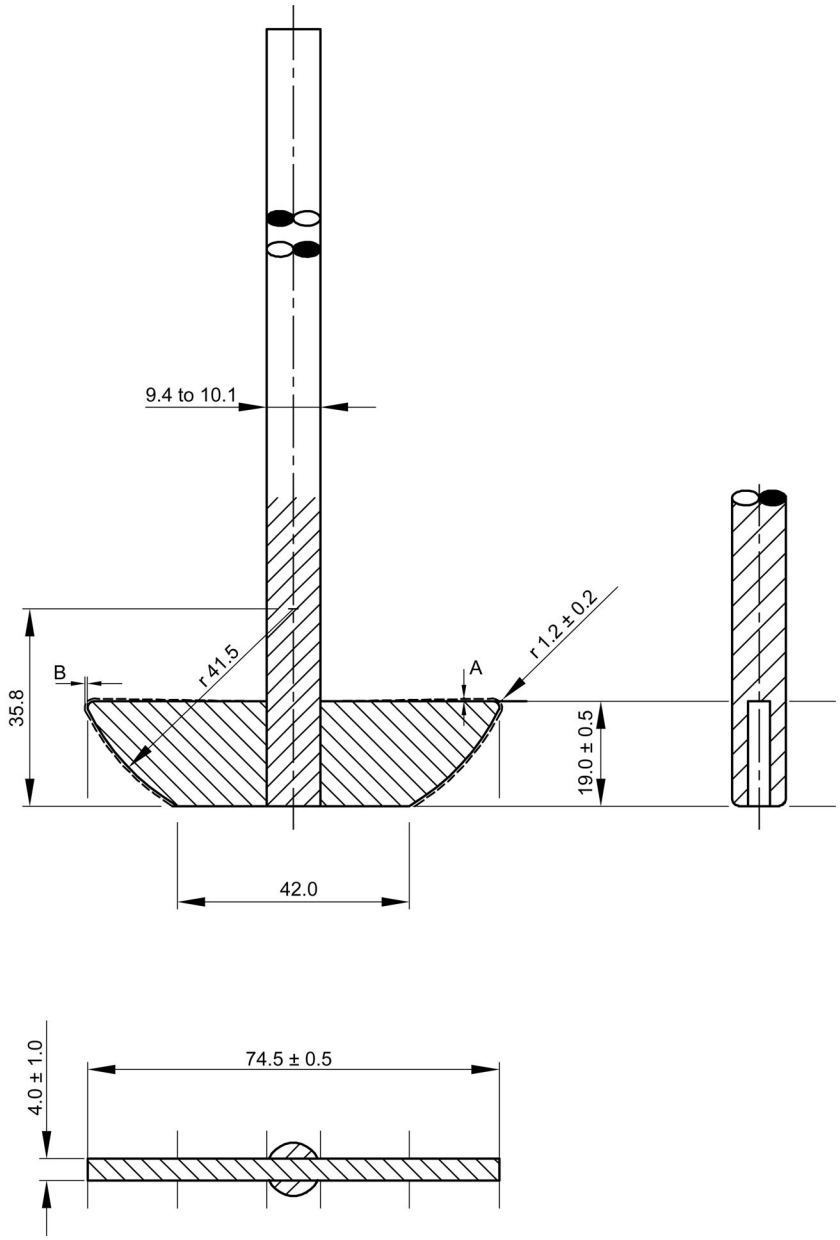


1) Screen with welded seam: 0.22-0.31 mm wire diameter with wire opening of 0.36-0.44 mm. After welding the screen may be slighty altered.

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

Figure 2.9.3.-1. – *Apparatus 1, Basket stirring element Dimensions in millimetres*

The apparatus uses a clamp mechanism and 2 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 must not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use suitably inert tubing, such as polytetrafluoroethylene, with a 1.6 mm inner diameter and inert flanged-end connections.



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

Apparatus suitability. The determination of suitability of the apparatus 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 (Apparatus 1 and 2), dip rate (Apparatus 3), and flow rate of medium (Apparatus 4).

Determine the acceptable performance of the dissolution test apparatus periodically.

PROCEDURE

APPARATUS 1 AND 2

Immediate-release dosage forms

Procedure. Place the stated volume of the dissolution medium (± 1 per cent) in the vessel of the specified apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 °C, and remove the thermometer. ◊The test may also be carried out with the thermometer in place, provided it is shown that results equivalent to those obtained without the thermometer are obtained.◊

Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit. Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a specimen 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. Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37 °C 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 at suitable times. Perform the analysis using a suitable assay method(5). Repeat the test with additional dosage units.

(5) Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active substance or contain extractable substances that would interfere with the analysis.

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

Dissolution medium. A suitable dissolution medium is used. The volume specified refers to measurements made between 20 °C and 25 °C. If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the specified pH. Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases must be removed prior to testing(6).

Time. 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. Samples are to be withdrawn only at the stated times, within a tolerance of ± 2 per cent.

Prolonged-release dosage forms

Procedure. Proceed as described for immediate-release dosage forms.

Dissolution medium. Proceed as described for immediate-release dosage forms.

Time. The test-time points, generally 3, are expressed in hours.

Delayed-release dosage forms

Procedure. Use Method A or Method B.

Method A

– *Acid stage*. Place 750 mL of *0.1 M hydrochloric acid* in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place 1 dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 h of operation in *0.1 M 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.

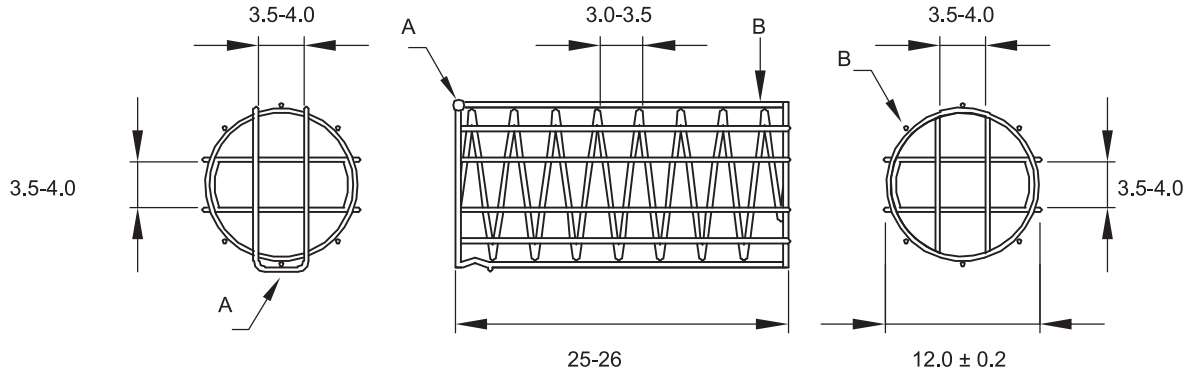
– *Buffer stage*. Complete the operations of adding the buffer and adjusting the pH within 5 min. With the apparatus operating at the rate specified, add to the fluid in the vessel 250 mL of a 0.20 M solution of *trisodium phosphate dodecahydrate R* that has been equilibrated to 37 ± 0.5 °C. Adjust, if necessary, with *2 M hydrochloric acid R* or *2 M sodium hydroxide R* to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 min, 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 M hydrochloric acid* in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate. After 2 h of operation in *0.1 M 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*. For this stage of the procedure use buffer that has previously been equilibrated to a temperature of 37 ± 0.5 °C. Drain the acid from the vessel and add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 3 volumes of *0.1 M hydrochloric acid* with 1 volume of a 0.20 M solution of *trisodium phosphate dodecahydrate R* and adjusting, if necessary, with *2 M hydrochloric acid R* or *2 M sodium hydroxide R* to a pH of 6.8 ± 0.05. This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel, containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 min, 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 per cent, unless otherwise specified.



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

Figure 2.9.3.-3. – *Alternative sinker*
Dimensions in millimetres

(6) A method of de-aeration is as follows: heat the medium, while stirring gently, to about 41 °C, 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 min. Other validated de-aeration techniques for removal of dissolved gases may be used.

APPARATUS 3

Immediate-release dosage forms

Procedure. Place the stated volume of the dissolution medium (± 1 per cent) in each vessel of the apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 °C, 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. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9-10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the medium from a zone midway between the surface of the dissolution medium and the bottom of each vessel. Perform the analysis as directed. If necessary, repeat the test with additional dosage units.

Replace the aliquot withdrawn for analysis with equal volumes of fresh dissolution medium at 37 °C 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 at suitable times.

Dissolution medium. Proceed as described for immediate-release dosage forms under Apparatus 1 and 2.

Time. Proceed as described for immediate-release dosage forms under Apparatus 1 and 2.

Prolonged-release dosage forms

Procedure. Proceed as described for immediate-release dosage forms under Apparatus 3.

Dissolution medium. Proceed as described for prolonged-release dosage forms under Apparatus 1 and 2.

Time. Proceed as described for prolonged-release dosage forms under Apparatus 1 and 2.

Delayed-release dosage forms

Procedure. Proceed as described for delayed-release dosage forms, Method B, under Apparatus 1 and 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 and 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, on a wire carrier. 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 ± 0.5 °C through the bottom of the cell to obtain the flow rate specified and measured with an accuracy of 5 per cent. 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 described for immediate-release dosage forms under Apparatus 1 and 2.

Time. Proceed as described for immediate-release dosage forms under Apparatus 1 and 2.

Prolonged-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 4.

Time. Proceed as described for immediate-release dosage forms under Apparatus 4.

Delayed-release dosage forms

Procedure. Proceed as described for delayed-release dosage forms under Apparatus 1 and 2, using the specified media.

Time. Proceed as described for delayed-release dosage forms under Apparatus 1 and 2.

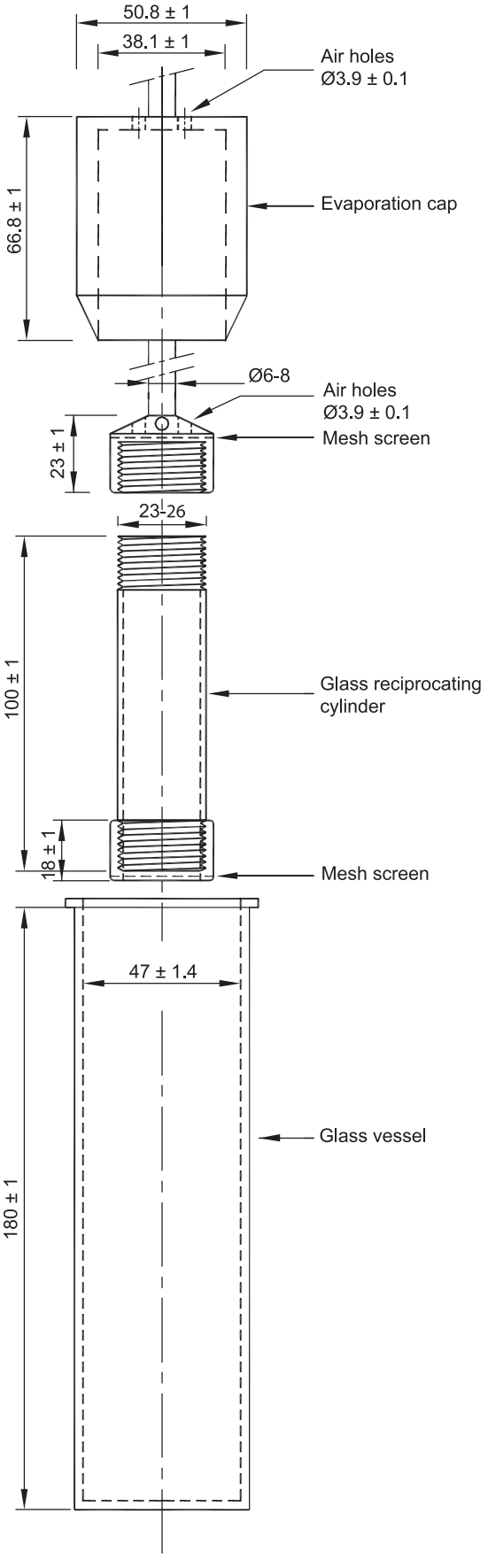


Figure 2.9.3.-4. – *Apparatus 3, glass vessel and reciprocating cylinder*

Dimensions in millimetres

INTERPRETATION

Immediate-release dosage forms

Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units tested conform to Table 2.9.3.-1. Continue testing through the 3 levels unless the results conform at either S_1 or S_2. The quantity Q, is the specified amount of dissolved active substance, expressed as a percentage of the labelled content; the 5 per cent, 15 per cent, and 25 per cent values in Table 2.9.3.-1 are percentages of the labelled content so that these values and Q are in the same terms.

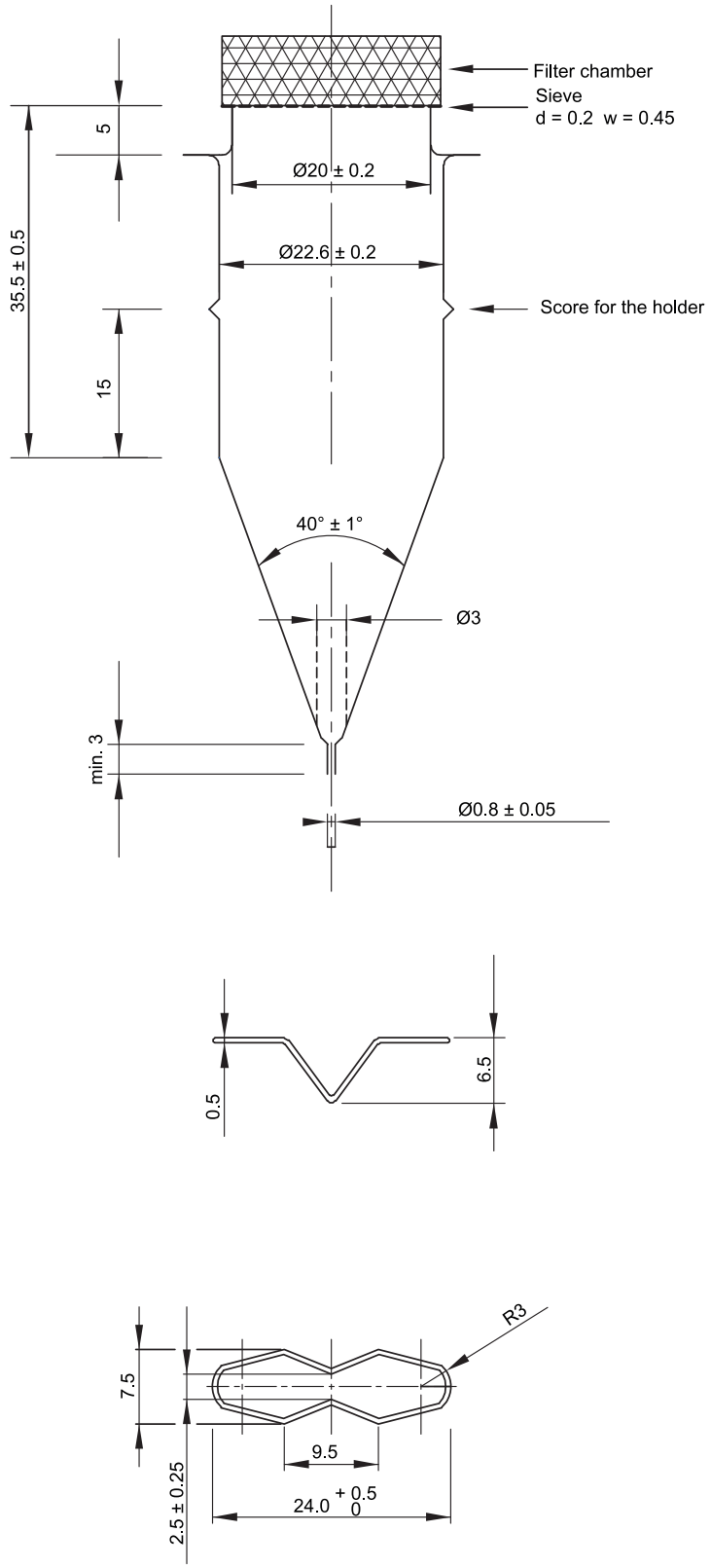


Figure 2.9.3.-5. – *Apparatus 4, large cell for tablets and capsules (top), tablet holder for the large cell (bottom)*

Dimensions in millimetres unless otherwise specified

Table 2.9.3.-1

Level	Number tested	Acceptance criteria
S_1	6	Each value is not less than Q + 5 per cent.
S_2	6	Average value of 12 dosage units (S_1 + S_2) is equal to or greater than Q, and no value is less than Q – 15 per cent.
S_3	12	Average value of 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 per cent, and no value is less than Q – 25 per cent.

Prolonged-release dosage forms

Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units tested conform to Table 2.9.3.-2. Continue testing through the 3 levels unless the results conform at either L_1 or L_2. Limits on the amounts of active substance dissolved are expressed in terms of the percentage of labelled 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.

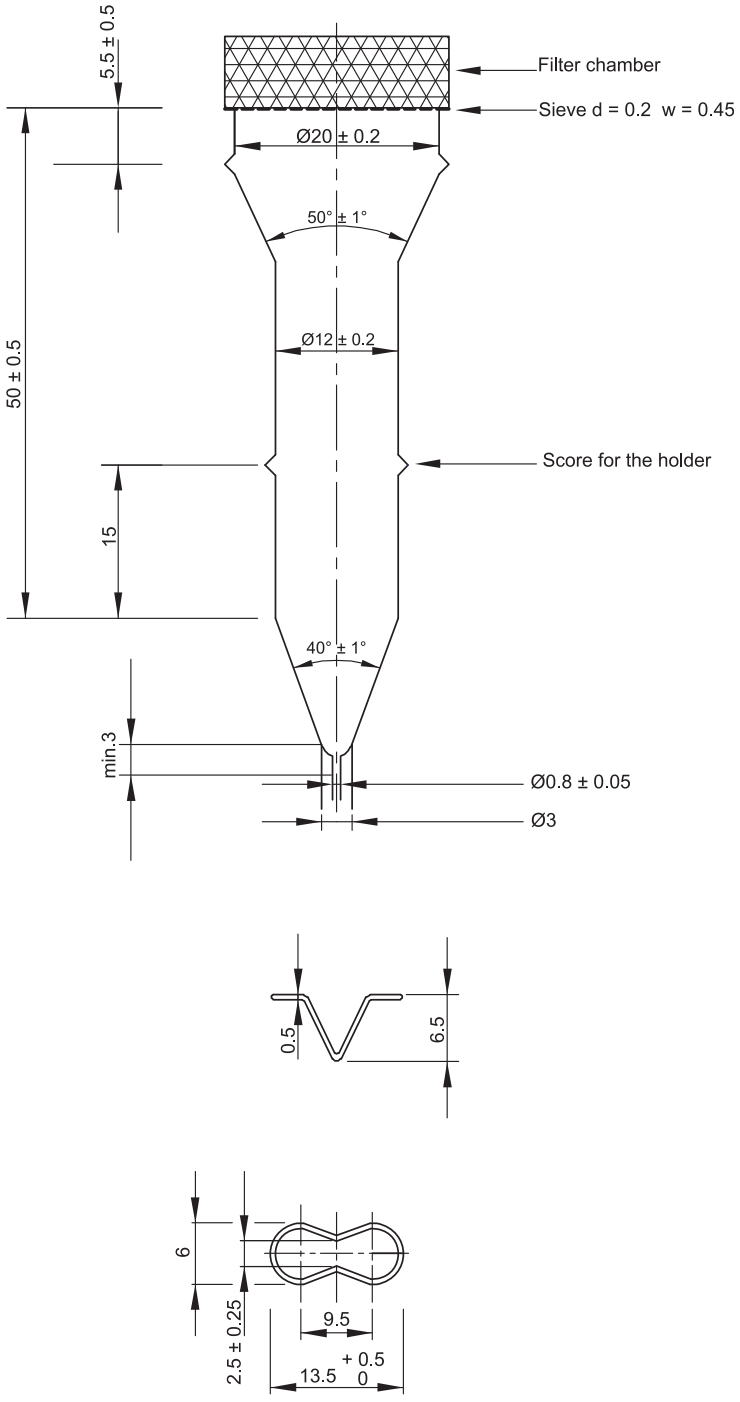


Figure 2.9.3.-6. – *Apparatus 4, small cell for tablets and capsules (top), tablet holder for the small cell (bottom)*

Dimensions in millimetres unless otherwise specified

Table 2.9.3.-2

Level	Number tested	Acceptance 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 per cent of labelled content outside each of the stated ranges; and no value is more than 10 per cent of labelled 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 per cent of labelled content outside each of the stated ranges; not more than 2 of the 24 values are more than 10 per cent of labelled content below the stated amount at the final test time; and no value is more than 20 per cent of labelled content outside each of the stated ranges or more than 20 per cent of labelled content below the stated amount at the final test time.

Delayed-release dosage forms

Acid stage. Unless otherwise specified, the requirements of this portion of the test are met if the quantities, based on the percentage of the labelled content, of active substance dissolved from the dosage units tested conform to Table 2.9.3.-3. Continue testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level.

Table 2.9.3.-3

Level	Number tested	Acceptance criteria
A_1	6	No individual value exceeds 10 per cent dissolved.
A_2	6	The average value of the 12 dosage units ($A_1 + A_2$) is not more than 10 per cent dissolved, and no value is greater than 25 per cent dissolved.
A_3	12	The average value of the 24 dosage units ($A_1 + A_2 + A_3$) is not more than 10 per cent dissolved, and no value is greater than 25 per cent dissolved.

Buffer stage. Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units tested conform to Table 2.9.3.-4. Continue testing through the 3 levels unless the results of both stages conform at an earlier level. The value of *Q* in Table 2.9.3.-4 is 75 per cent dissolved unless otherwise specified. The quantity, *Q*, is the specified total amount of active substance dissolved in both the acid and buffer stages, expressed as a percentage of the labelled content. The 5 per cent, 15 per cent and 25 per cent values in Table 2.9.3.-4 are percentages of the labelled content so that these values and *Q* are in the same terms.

Table 2.9.3.-4

Level	Number tested	Acceptance criteria
B_1	6	No value is less than Q + 5 per cent.
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 per cent.
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 per cent, and no value is less than Q – 25 per cent.

Recommendations on dissolution testing are given in general chapter 5.17.1.

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2.9.4. DISSOLUTION TEST FOR PATCHES

This test is used to determine the dissolution rate of the active substance(s) of patches.

The disk assembly method, the cell method or the rotating cylinder method may be used, as suitable, according to the composition, dimensions and shape of the patch. A membrane may be used for the purpose of the test. The membrane material (inert porous cellulose, silicone, etc.) must not affect the release kinetics of the active substance(s) from the patch. It must also be free of substances that may interfere with the performance of the patch (e.g. grease). The membrane may be suitably treated before the tests, for example by maintaining it for 24 h in the medium to be used in the test. The membrane is applied over the release surface of the patch in such a way as to avoid the formation of air bubbles.

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).

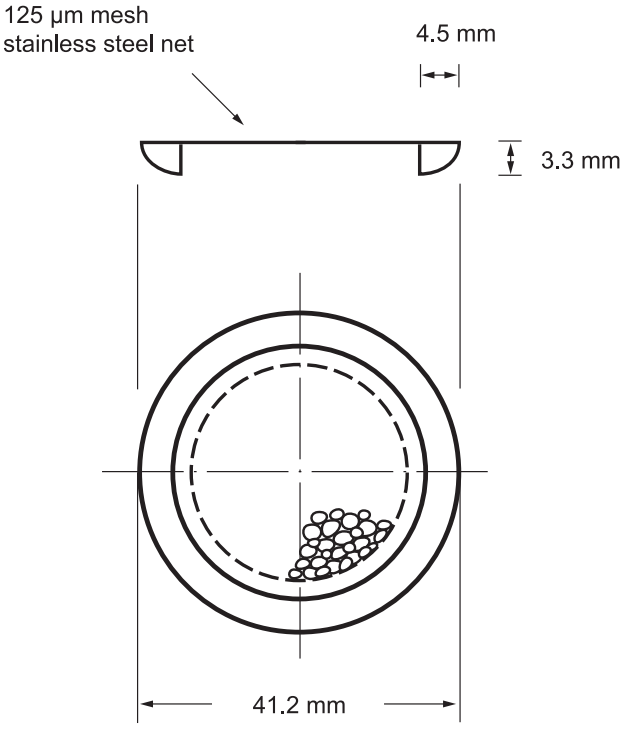


Figure 2.9.4.-1. – *Disk assembly*

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 facing upwards 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.