

beaker with a capacity of at least 4 litres filled with 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 litres. 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.

Method. Use three suppositories or pessaries. Place each one on the lower disc of a device, place the latter in the sleeve and secure. Invert the apparatuses every 10 min. Examine the samples after the period prescribed in the monograph. To pass the test all the samples must have disintegrated.

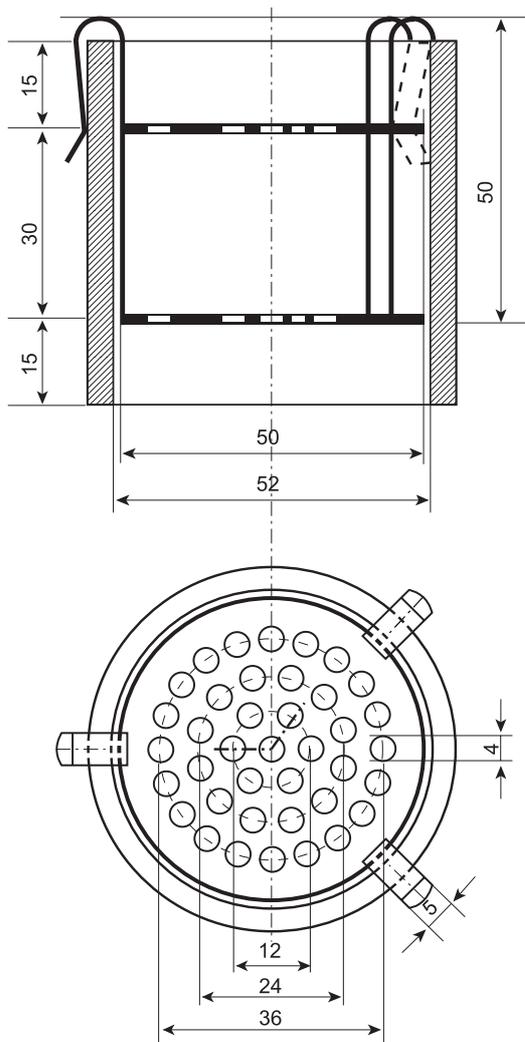
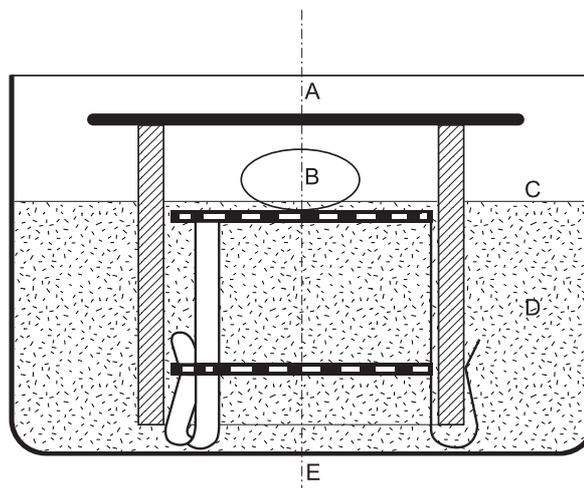


Figure 2.9.2-1. – Apparatus for disintegration of suppositories and pessaries
Dimensions in millimetres

METHOD OF OPERATION FOR VAGINAL TABLETS

Use the apparatus described above, arranged so as to rest on the hooks (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 at 36-37 °C until a uniform film covers the perforations of the disc. Use three vaginal tablets. Place each one on the upper plate of an apparatus and cover the latter with a glass plate to maintain appropriate conditions of humidity. Examine the state of the samples after the period prescribed in the monograph. To pass the test all the samples must have disintegrated.



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

Figure 2.9.2-2.

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2.9.3. DISSOLUTION TEST FOR SOLID DOSAGE FORMS

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⁽¹⁾; 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 preparation and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and a capacity of 1 litre. 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⁽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 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.

(1) The materials must not sorb, react, or interfere with the preparation to be tested.

(2) If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of samples.

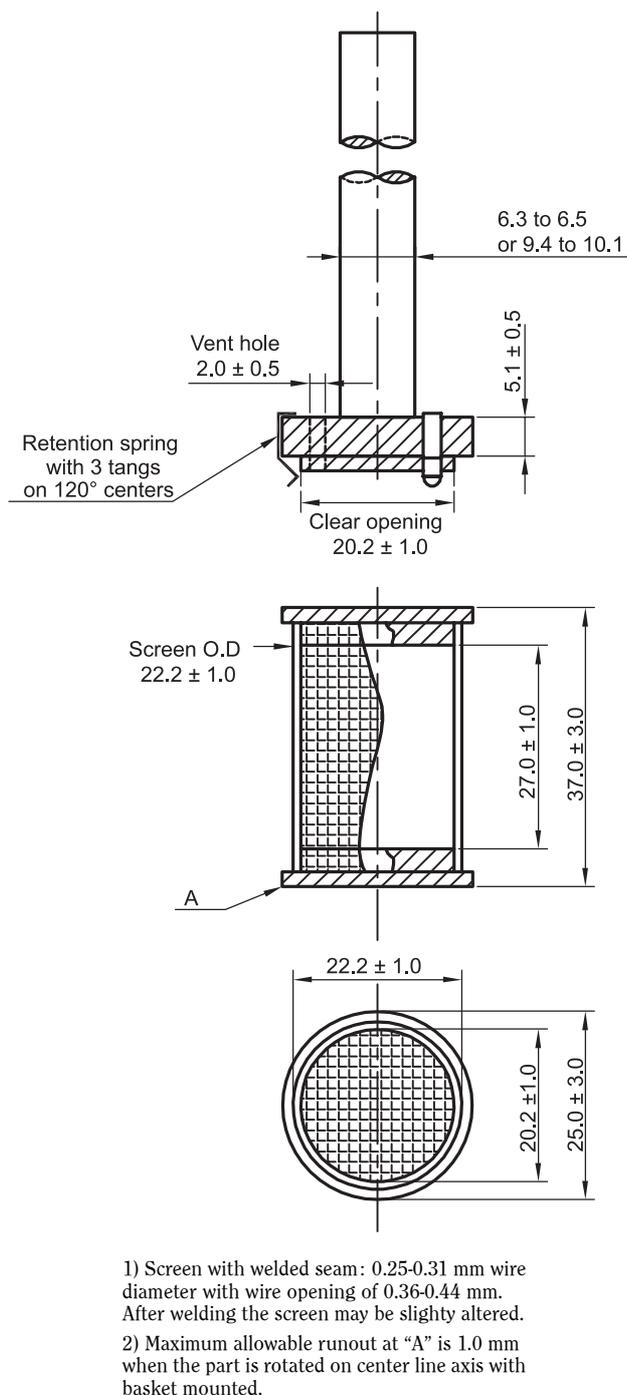


Figure 2.9.3-1. – Apparatus 1, Basket stirring element
Dimensions in millimetres

A basket having a gold coating of about $2.5 \mu\text{m}$ (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.

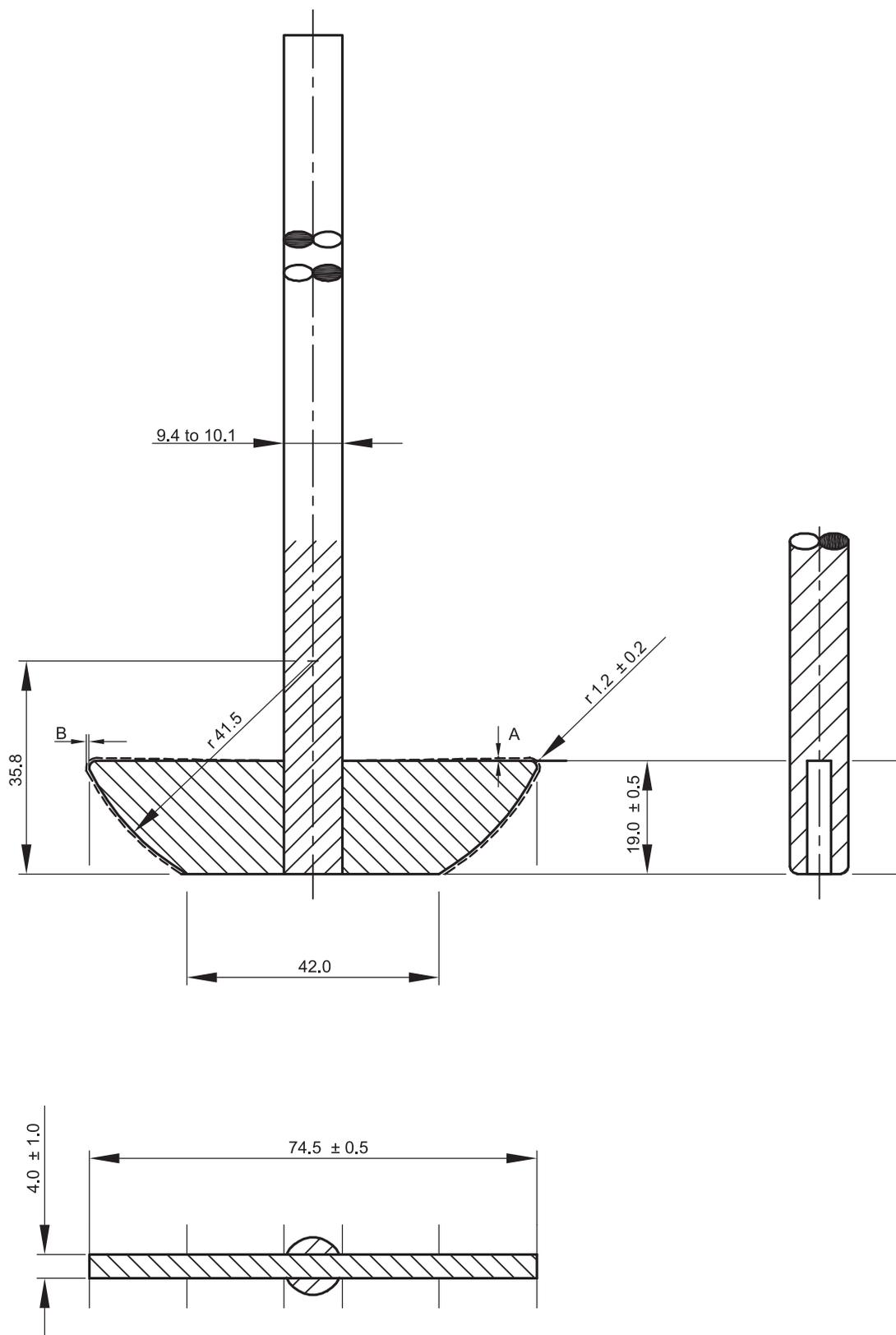
Apparatus 3 (Reciprocating cylinder). The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material) and screens that are made of suitable nonsorbing and nonreactive material, and 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 preparations 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. Non-pulsated flow may also be used.

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. The apparatus uses a clamp mechanism and 2 O-rings for the fixation of the cell assembly. 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.

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



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

volume and temperature of the dissolution medium, rotation speed (Apparatus 1 and 2, dip rate (Apparatus 3), and flow rate of medium (Apparatus 4).

PROCEDURE

APPARATUS 1 AND 2

Conventional-release solid 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⁽³⁾. Repeat the test with additional dosage units.

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⁽⁴⁾.

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 solid dosage forms

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

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

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

Delayed-release solid dosage forms

Procedure. Use Method A or Method B.

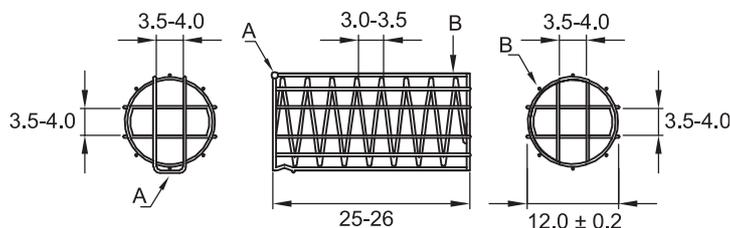
Method A

- **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 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 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

(3) 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.

(4) A method of deaeration 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 deaeration techniques for removal of dissolved gases may be used.

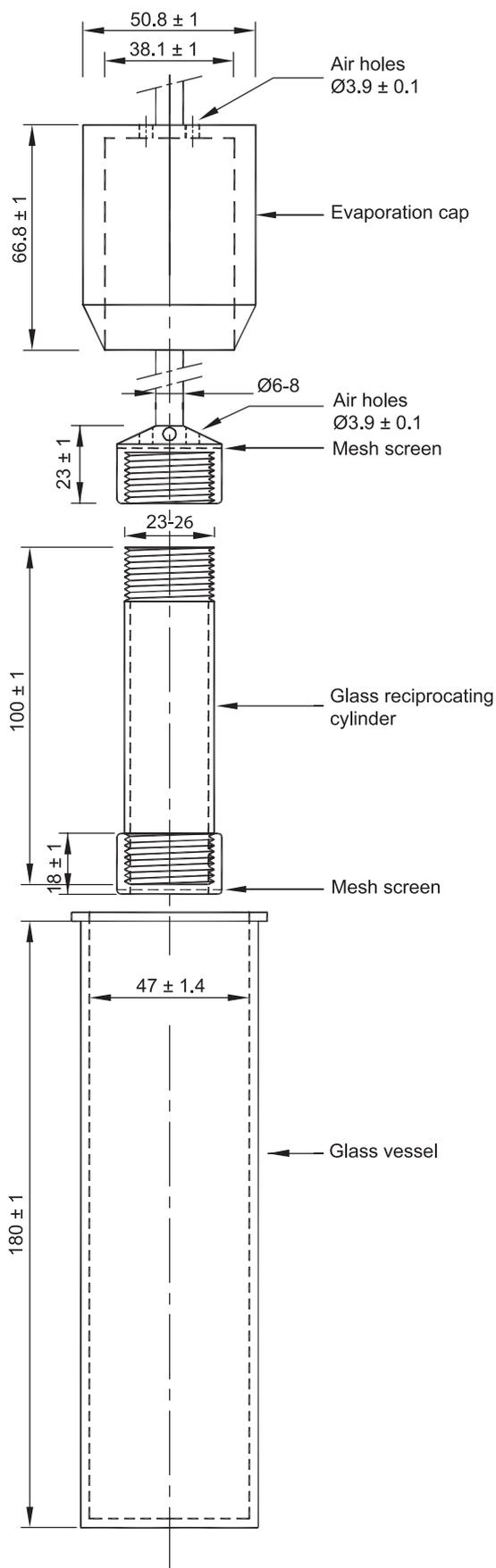


Figure 2.9.3-4. – Apparatus 3, glass vessel and reciprocating cylinder
Dimensions in millimetres unless otherwise specified

APPARATUS 3

Conventional-release solid 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 conventional-release dosage forms under Apparatus 1 and 2.

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

Prolonged-release dosage forms

Procedure. Proceed as described for conventional-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

Conventional-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 conventional-release dosage forms under Apparatus 1 and 2.

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

Prolonged-release dosage forms

Procedure. Proceed as described for conventional-release dosage forms under Apparatus 4.

Dissolution medium. Proceed as described for conventional-release dosage forms under Apparatus 4.

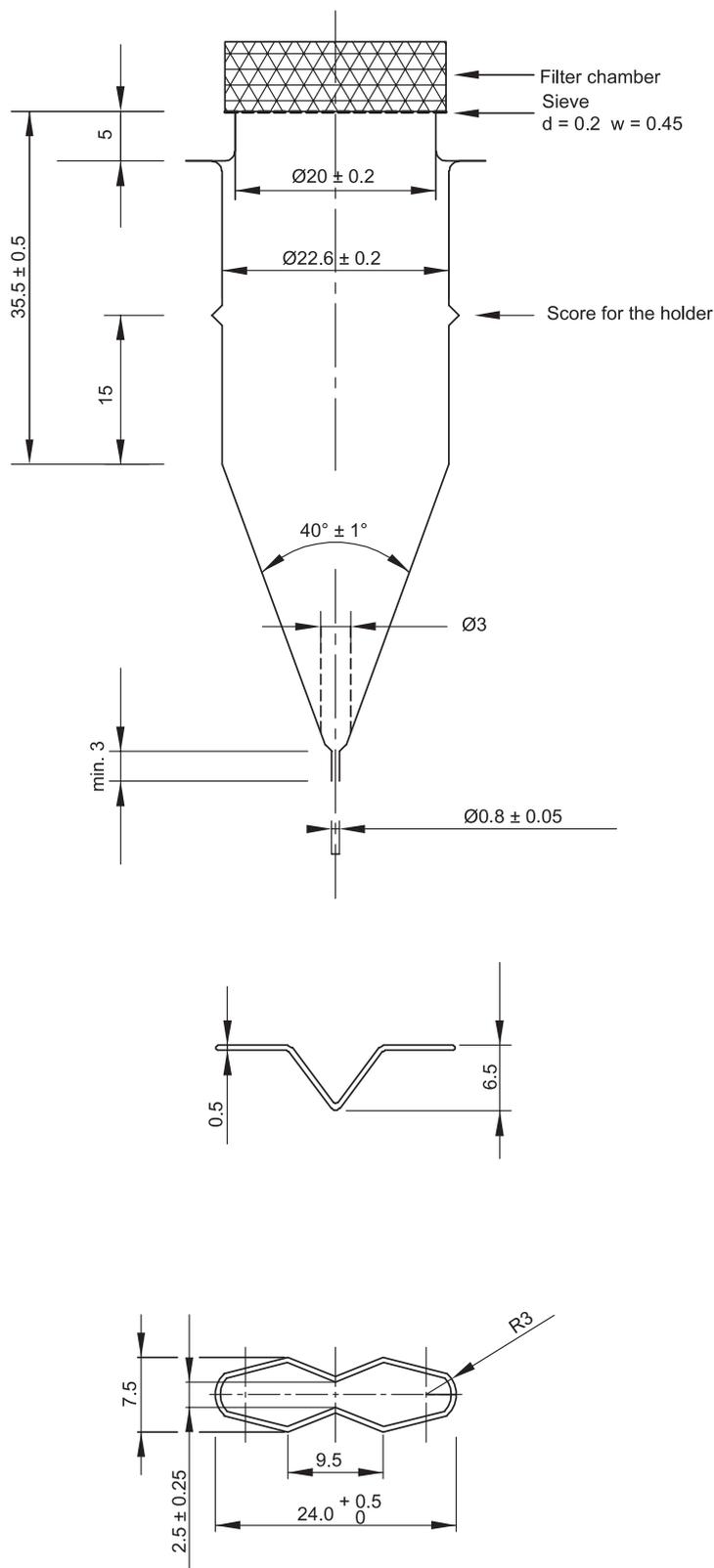


Figure 2.9.3-5. – Apparatus 4, large cell for tablets and capsules (top), tablet holder for the large cell (bottom) Dimensions in millimetres unless otherwise specified

Time. Proceed as described for conventional-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.

INTERPRETATION

Conventional-release solid 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

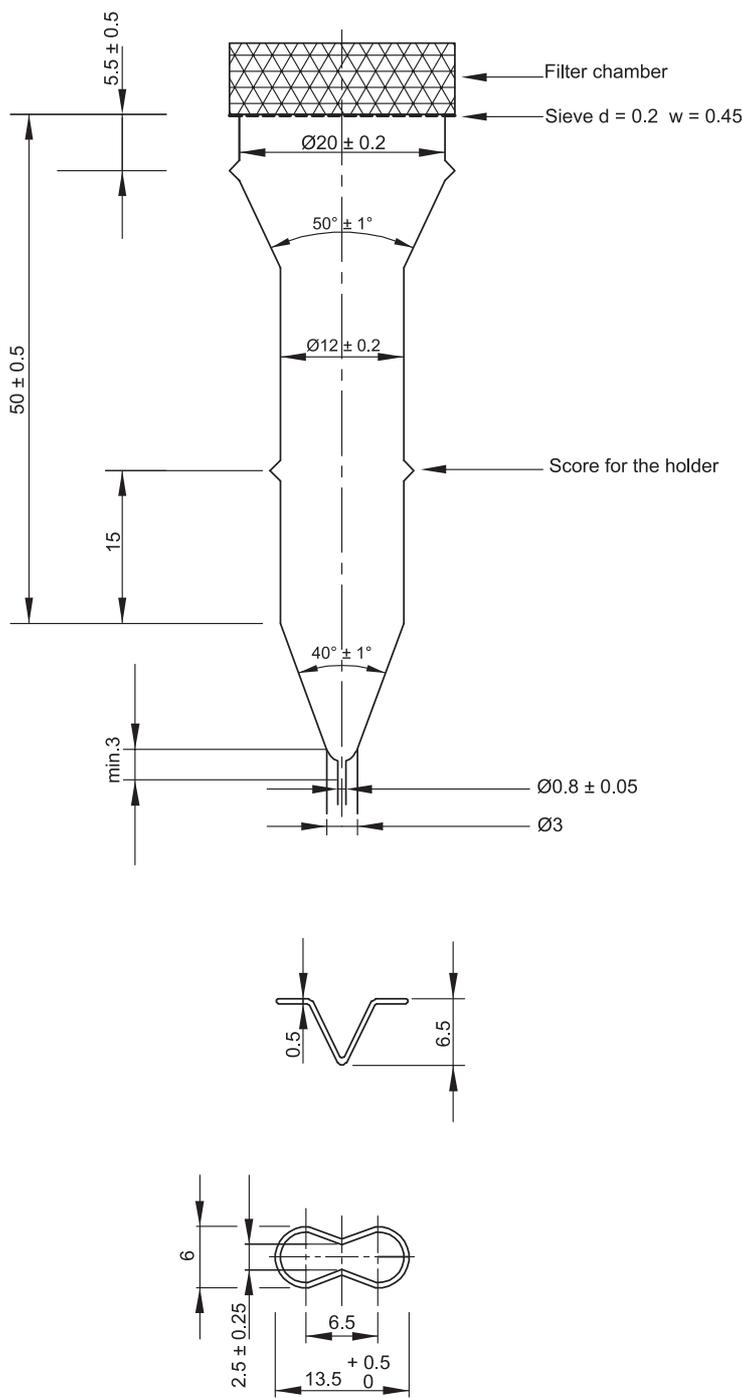


Figure 2.9.3-6. – Apparatus 4, small cell for tablets and capsules (top), tablet holder for the small cell (bottom)
 Dimensions in millimetres unless otherwise specified

labelled content; the 5 per cent, 15 per cent, and 25 per cent values in the Table are percentages of the labelled content so that these values and Q are in the same terms.

Table 2.9.3-1

Level	Number tested	Acceptance criteria
S_1	6	Each unit is not less than $Q + 5$ per cent.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q , and no unit is less than $Q - 15$ per cent.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q , not more than 2 units are less than $Q - 15$ per cent, and no 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.

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 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; none is more than 10 per cent of labelled content outside each of the stated ranges; and none 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 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 units are more than 10 per cent of labelled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 per cent of labelled content below the stated amount at the final test time; and none of the units 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 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 units ($A_1 + A_2$) is not more than 10 per cent dissolved, and no individual unit is greater than 25 per cent dissolved.
A_3	12	The average value of the 24 units ($A_1 + A_2 + A_3$) is not more than 10 per cent dissolved, and no individual unit 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 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 the Table 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 unit is less than $Q + 5$ per cent.
B_2	6	The average value of the 12 units ($B_1 + B_2$) is equal to or greater than Q , and no unit is less than $Q - 15$ per cent.
B_3	12	The average value of the 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q , not more than 2 units are less than $Q - 15$ per cent, and no unit is less than $Q - 25$ per cent.

The following section is published for information

Guidance on dissolution testing

In the determination of the dissolution rate of the active substance(s) of a solid dosage form, the following are to be specified:

- the apparatus to be used, and in cases where the flow-through apparatus is specified, which flow-through cell is to be used;
- the composition, the volume and the temperature of the dissolution medium;
- the rotation speed or the flow rate of the dissolution medium;
- the time, the method and the amount for sampling of the test solution or the conditions for continuous monitoring;
- the method of analysis;
- the acceptance criteria.

The choice of apparatus to be used depends on the physico-chemical characteristics of the dosage form. When a large quantity of dissolution medium is required to ensure sink conditions, or when a change of pH is necessary, the flow-through apparatus may be preferred.

EXPERIMENTAL TESTING CONDITIONS

The use of the basket and the paddle apparatus and the reciprocating cylinder apparatus is generally based on the principle of operating under "sink conditions", i.e. in such a manner that the material already in solution does not exert a significant modifying effect on the rate of dissolution of the remainder. "Sink conditions" normally occur in a volume of dissolution medium that is at least 3 to 10 times the saturation volume.

In general, an aqueous medium is used. The composition of the medium is chosen on the basis of the physico-chemical characteristics of the active substance(s) and excipient(s) within the range of conditions to which the dosage form is likely to be exposed after its administration. This applies in particular to the pH and the ionic strength of the dissolution medium.

The pH of the dissolution medium is usually set between pH 1 and 8. In justified cases, a higher pH may be needed. For the lower pH values in the acidic range, 0.1 M hydrochloric acid is normally used. Recommended dissolution media are described hereafter.

Water is recommended as a dissolution medium only when it is proven that the pH variations do not have an influence on the dissolution characteristics.

In specific cases, dissolution media may contain enzymes, surfactants, further inorganic substances and organic substances. For the testing of preparations containing poorly aqueous-soluble active substances, modification of the medium may be necessary. In such circumstances, a low concentration of surfactant is recommended; it is recommended to avoid the use of organic solvents.

Gases dissolved in the dissolution medium can affect the results of the dissolution test. This is true, in particular, for the flow-through apparatus where de-aeration of the medium is necessary to avoid the formation of gas bubbles in the flow-through cell. A suitable method of de-aeration is as follows: heat the medium while stirring gently to about 41 °C, immediately filter under vacuum using a filter with a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 min. Other de-aeration techniques for removal of dissolved gases may be used.

Using the paddle or basket apparatus, the volume of dissolution medium is normally 500-1000 ml. A stirring speed of between 50 r/min and 100 r/min is normally chosen; it must not exceed 150 r/min.

For the flow-through apparatus, the liquid flow rate is normally set between 4 ml/min and 50 ml/min.

RECOMMENDED DISSOLUTION MEDIA

The following dissolution media may be used.

Table 2.9.3-5. – Examples of dissolution media

pH	Dissolution media
pH 1.0	HCl
pH 1.2	NaCl, HCl
pH 1.5	NaCl, HCl
pH 4.5	Phosphate or acetate buffer
pH 5.5 and 5.8	Phosphate or acetate buffer
pH 6.8	Phosphate buffer
pH 7.2 and 7.5	Phosphate buffer

The composition and preparation of these various media are indicated below.

Hydrochloric acid media

- 0.2 M hydrochloric acid,
- 0.2 M sodium chloride. Dissolve 11.69 g of sodium chloride R in water R and dilute to 1000.0 ml with the same solvent.

For preparing media with the following pH, place 250.0 ml of 0.2 M sodium chloride in a 1000 ml volumetric flask, add the specified volume of 0.2 M hydrochloric acid, then dilute to 1000.0 ml with water R (see Table 2.9.3-6.).

The hydrochloric acid media may also be prepared by replacing sodium chloride by potassium chloride.

Acetate buffer solutions

- 2 M acetic acid. Dilute 120.0 g of glacial acetic acid R to 1000.0 ml with water R.
- Acetate buffer solution pH 4.5. Dissolve 2.99 g of sodium acetate R in water R. Add 14.0 ml of 2 M acetic acid and dilute to 1000.0 ml with water R.
- Acetate buffer solution pH 5.5. Dissolve 5.98 g of sodium acetate R in water R. Add 3.0 ml of 2 M acetic acid and dilute to 1000.0 ml with water R.
- Acetate buffer solution pH 5.8. Dissolve 6.23 g of sodium acetate R in water R. Add 2.1 ml of 2 M acetic acid and dilute to 1000.0 ml with water R.

Phosphate buffer solutions

For preparing buffers with the pH values indicated in Table 2.9.3-7, place 250.0 ml of 0.2 M potassium dihydrogen phosphate R in a 1000 ml volumetric flask, add the specified volume of 0.2 M sodium hydroxide, then dilute to 1000.0 ml with water R.

Other phosphate buffer solutions

- Phosphate buffer solution pH 4.5. Dissolve 13.61 g of potassium dihydrogen phosphate R in 750 ml of water R. Adjust the pH (2.2.3) if necessary with 0.1 M sodium hydroxide or with 0.1 M hydrochloric acid. Dilute to 1000.0 ml with water R.
- Phosphate buffer solution pH 5.5 R.
- Phosphate buffer solution pH 6.8 R1.

- Buffer solution pH 7.2 R.
- 0.33 M phosphate buffer solution pH 7.5 R.

Table 2.9.3-7. – Phosphate buffer solutions

pH	5.8	6.0	6.2	6.4	6.6	6.8
NaOH (ml)	18.0	28.0	40.5	58.0	82.0	112.0
pH	7.0	7.2	7.4	7.6	7.8	8.0
NaOH (ml)	145.5	173.5	195.5	212.0	222.5	230.5

Simulated intestinal fluid pH 6.8

Mix 250.0 ml of a solution containing 6.8 g of potassium dihydrogen phosphate R, 77.0 ml of 0.2 M sodium hydroxide and 500 ml of water R. Add 10.0 g of pancreas powder R, mix and adjust the pH (2.2.3), if necessary. Dilute to 1000.0 ml with water R.

Artificial gastric juice

Dissolve 2.0 g of sodium chloride R and 3.2 g of pepsin powder R in water R. Add 80 ml of 1 M hydrochloric acid and dilute to 1000.0 ml with water R. If required, pepsin powder may be omitted.

Increasing pH

For a test involving increasing pH, one of the following sequences may be used:

Time (h)	0 - 1	1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7
pH	1.0							
pH	1.2	6.8						
pH	1.2	2.5	4.5	7.0		7.5		
pH	1.5	4.5			7.2			

To achieve this pH variation, it is possible either:

- to substitute one buffer solution for another (whole substitution);
- to remove only half of the medium each time (half change method) and replace it with a buffer solution of higher pH: the initial pH is 1.2 and the second solution is phosphate buffer solution pH 7.5;
- to an initial solution at pH 1.5, add a dose of a powder mixture containing tris(hydroxymethyl)aminomethane R and anhydrous sodium acetate R to obtain pH 4.5 and a second dose to obtain pH 7.2, as described below:
 - hydrochloric acid pH 1.5. Dissolve 2 g of sodium chloride R in water R, add 31.6 ml of hydrochloric acid R and dilute to 1000.0 ml with water R;
 - buffer solution pH 4.5. Mix 2.28 g of tris(hydroxymethyl)aminomethane R with 1.77 g of anhydrous sodium acetate R. Dissolve this mixture in the hydrochloric acid solution pH 1.5 described above;
 - buffer solution pH 7.2. Mix 2.28 g of tris(hydroxymethyl)aminomethane R with 1.77 g of anhydrous sodium acetate R. Dissolve this mixture in the buffer solution pH 4.5 described above.

The flow-through cell may be used for the continuous change of pH.

Table 2.9.3-6. – Hydrochloric acid media

pH	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
HCl (ml)	425.0	336.0	266.0	207.0	162.0	130.0	102.0	81.0	65.0	51.0	39.0

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).

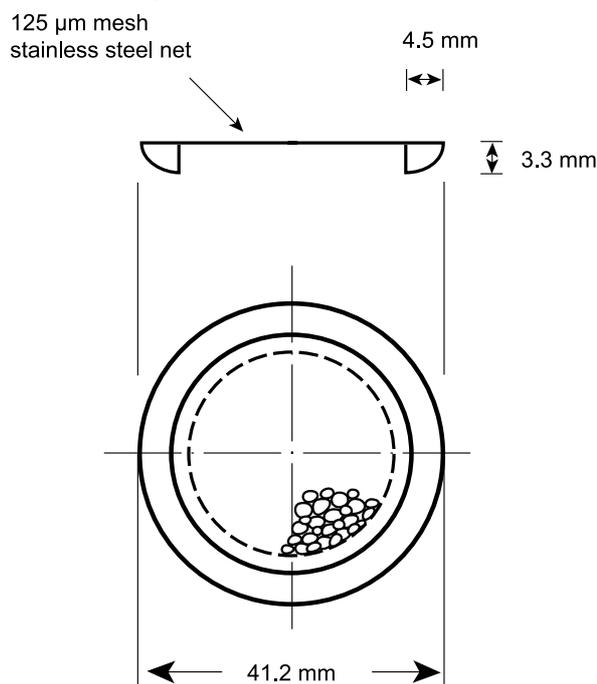


Figure 2.9.4.-1. – Disk assembly

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