2.5.2. Dissolution

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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Change **to:**

2.5.2. Dissolution

This General Chapter has been harmonized with corresponding texts of the European Pharmacopoeia, the Japanese Pharmacopoeia and the United Pharmacopoeia. Portion of the IP text that and not part of the PDG harmonized text, are marked with symbols (♦ ♦).

~~This test is designed to determine compliance with the dissolution requirements for solid, semi solid and suspension dosage forms.~~

~~Use Apparatus 2 (Paddle) unless otherwise directed. All parts of the apparatus that may come into contact with the preparation under examination or with the dissolution medium are chemically inert and do not adsorb, react or interfere with the preparation under examination. All metal parts of the apparatus that may come into contact with the preparation or the dissolution medium must be made from stainless steel, type 316 or equivalent or coated with a suitable material to ensure that such parts do not react or interfere with the preparation under examination or the dissolution medium.~~

~~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 element.~~

~~An apparatus that permits observation of the preparation under examination and the stirrer during the test is preferable~~

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~~ one tablet or ~~1~~one capsule or the amount specified.

♦For dosage forms containing or coated with gelatin that do not conform to the dissolution specification, repeat the test as follows.

Dissolution Medium with pH 4.0 or less

Enzyme. Pepsin, activity determined by the Assay test in the monograph for Pepsin.

Amount. A quantity of pepsin that results in an activity of not more than 7,50,000 Units per litre of dissolution medium.

Dissolution Medium with more than pH 4.0 and less than 6.8

Enzyme. Papain, activity determined by the Assay test in the monograph for Papain or Bromelain, activity determined by the procedure in bromelain under general reagents.

Amount. A quantity of papain that results in an activity of not more than 5,50,000 Units per litre of dissolution medium or a quantity of bromelain that results in an activity of not more than 30 gelatin–digesting units (GDU) per litre of dissolution medium.

Dissolution Medium with pH 6.8 or more

Enzyme. Pancreatin, protease activity determined by the procedure in Assay for protease activity in the monograph for Pancreatin.

Amount. A quantity of pancreatin that results in a protease activity of not more than 2000 Units per litre of dissolution medium.

NOTE — Appropriate organic solvent(s) may be used to enhance drug solubility for the preparation of the reference standard solutions. However, not more than 5 per cent (v/v) of the organic solvent should be present in the final solution unless validated.♦

Apparatus 1 (Basket Apparatus)

~~An assembly consisting of the following:~~

- ~~A cylindrical vessel, A, made of borosilicate glass or any other suitable transparent material, with a hemispherical bottom and with a nominal capacity of 1000 ml unless otherwise specified in the individual monograph and an inside diameter of 98–106 mm (Fig.2.5.2–1). The vessel has a flanged upper rim and is fitted with a lid that has a number of openings, one of which is central. Modified peak vessels can be used to eliminate coning. In addition to vessel parameters like inner diameter and height, evaluate parameters like hemisphere radius (49 mm to53 mm).~~

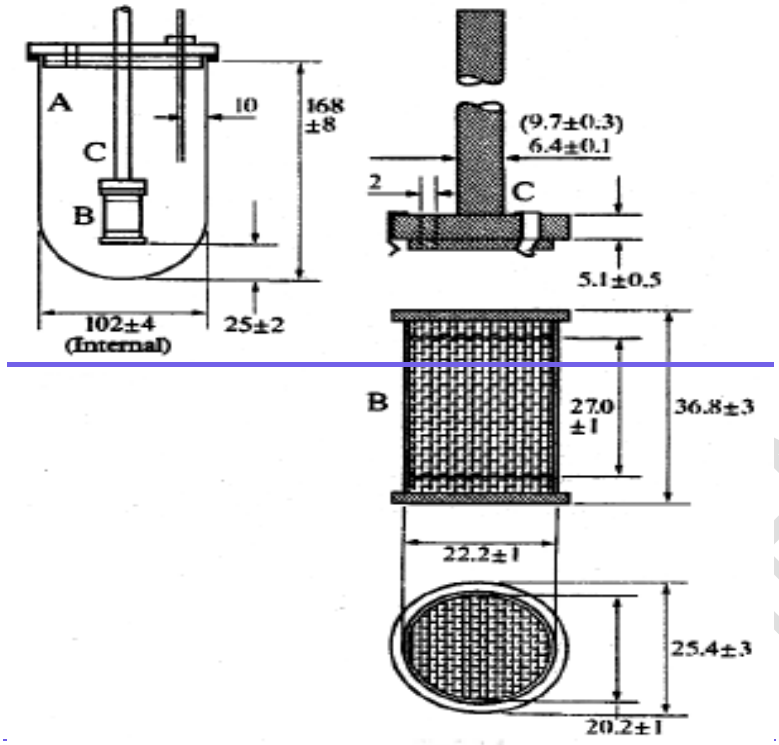
b. ~~A motor with a speed regulator capable of maintaining the speed of rotation of the serialized basket within 4 per cent of that specified in the individual monograph. The motor is fitted with a serialised basket, B (see Fig.2.5.2–2).The metallic shaft rotates smoothly and without significant wobble. The basket consists of two components. The top part, with a vent,~~

~~is attached to the shaft C, it is fitted with three spring clips, or other suitable means like o-rings, that allow removal of the lower part for introduction of the preparation under examination and that firmly hold the lower part of the basket concentric with the axis of the vessel during rotation. The lower detachable part of the basket is made of welded steam cloth, with a wire thickness of 0.265 ±0.045 mm diameter and with 0.4 ±0.04 mm square openings unless otherwise specified in the individual monograph, formed into a cylinder with narrow rim of sheet metal around the top and the bottom. Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or any other inert material. The basket may be plated with a 2.5 µm layer of gold for use with acidic media. The distance between the inside bottom of the vessel and the basket is maintained at 23 to 27 mm during the test. Evaluate the basket mesh integrity by using a magnifying glass or microscope at regular intervals.~~

~~c. A water bath or any other suitable heating device, such as a heating jacket set to maintain the dissolution medium at 36.5º to 37.5º. The bath liquid is kept in constant and smooth motion during the test. The vessel is securely clamped in the water bath in such a way that the displacement vibration from other equipment, including the water circulation device, is minimised.~~

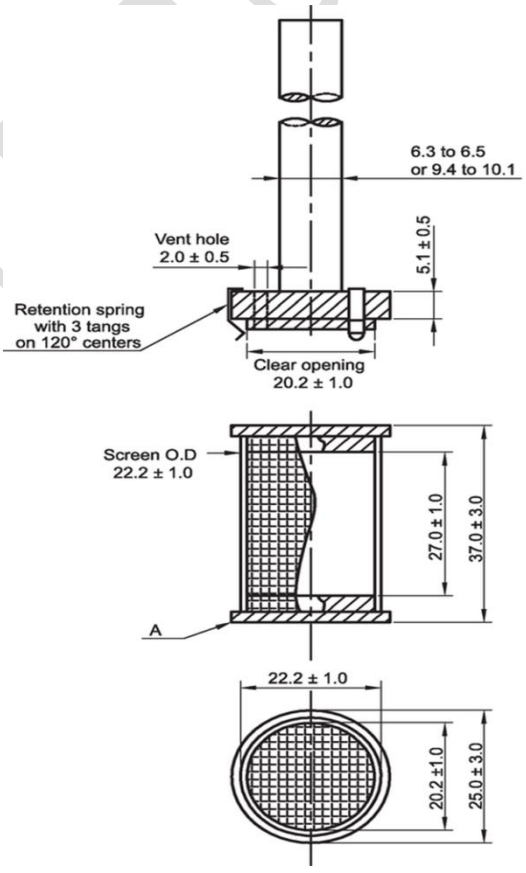
The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, preferably transparent material[1]; a motor; a drive shaft; and a cylindrical basket. The vessel is partially immersed in a water-bath or heated by a suitable device such as a heating jacket. The water-bath or heating device permits maintaining the temperature of the dissolution medium inside the vessel at ~~37.0±5°~~36.5º to 37.5º 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~~ 1000 ml. Its height is 160 to 210 mm and its inside diameter is 98 to 106 mm, ♦for a nominal capacity of ~~2 L~~2000 ml, the height is 280 to 300 mm, and its inside diameter is 98 to 106 mm; and for a nominal capacity of ~~4 L~~ 4000 ml, the height is 280 to 300 mm, and its inside diameter is 145 to155 mm♦. Its sides may be 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 other inert material, to the specifications shown in (Fig. 2.5.2-1). A basket having a gold coating or other inert material having a thickness not more than 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~~ 23 to 27 mm during the test.



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

[2]If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of aliquots of the solution under test and it minimizes the possible loss of medium.



(Dimensions in mm)

Fig. 2.5.2-1: Basket stirring element

1) Screen with welded seam: 0.22-0.31 mm wire diameter with aperture 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.

♦**Dissolution medium**. Use the dissolution medium specified in the individual monograph. If the medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the pH specified in the monograph. The dissolution medium should be deaerated prior to testing.

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

Filter suitability. It may be accomplished by preparing a suitable ~~standard~~ reference solution or a completely dissolved ~~sample~~ test solution (e.g., prepared as a typical ~~sample~~ test in a vessel or a ~~sample~~ test put in a beaker and stirred with a magnetic stirrer for 1 hour). For ~~standard~~ reference solution, compare the results for filtered solution (after discarding the appropriate volume) to those for the unfiltered solution. For ~~sample~~ test solution, compare the results for filtered solution (after discarding the appropriate volume) to those for centrifuged, unfiltered solution. ♦

Apparatus 2 (Paddle Apparatus)

~~The assembly is the same as in Apparatus 1 except that the stirring element consists of a drive shaft and blade forming a paddle, D (Fig.2.5.2-3 and Fig. 2.5.2-4) The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The shaft is positioned so that its axis is within 2 mm of the axis of the vessel and the lower edge of the blade is 23 to 27 mm from the inside bottom of the vessel. The apparatus operates in such a way that the paddle rotates smoothly and without significant wobble.~~

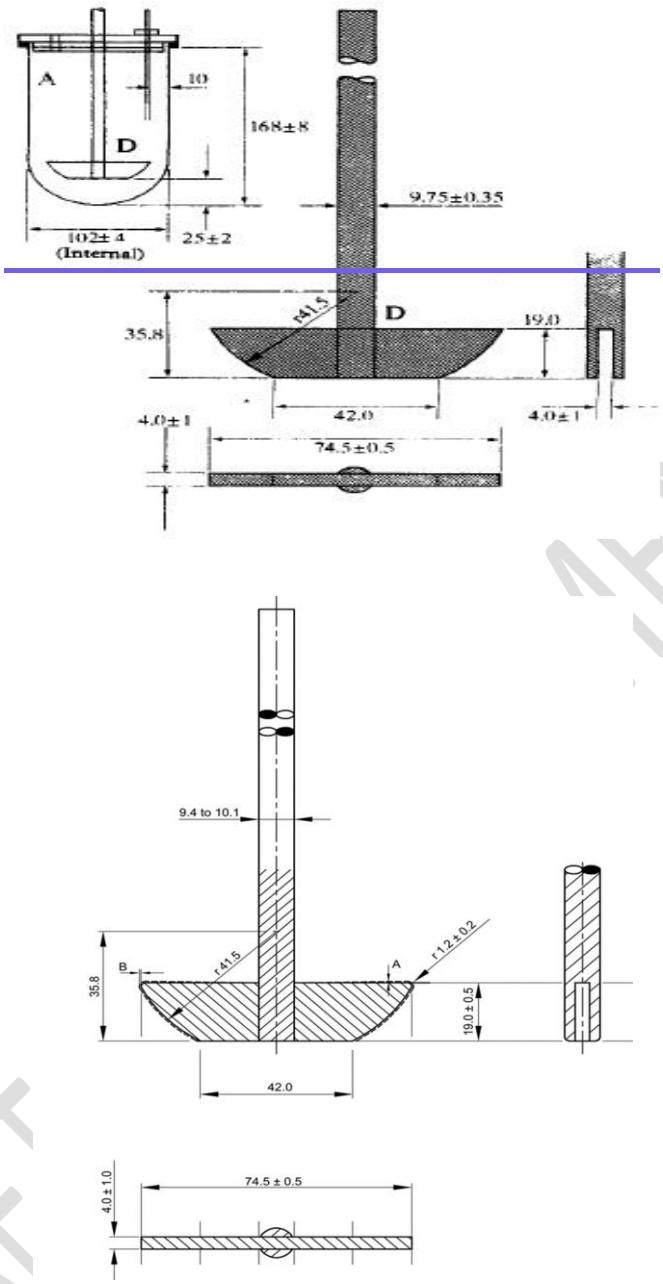
~~A water bath or any other suitable heating device, such as a heating jacket set to maintain the dissolution medium at 36.5º to 37.5º. The bath liquid is kept in constant and smooth motion during the test. The vessel is secured in the water bath in such a way that the displacement vibration from other equipment, including the water circulation device, is minimised.~~

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 (Fig. 2.5.2-2). The distance of ~~25±2 mm~~ 23 to 27 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 nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. Other suitable sinker devices may be used for example the one shown in (Fig. 2.5.2-~~3~~2a).

♦**Dissolution medium**. Proceed as directed under Apparatus 1.

Time. Proceed as directed under Apparatus 1.

Filter suitability. Proceed as directed under Apparatus 1.♦

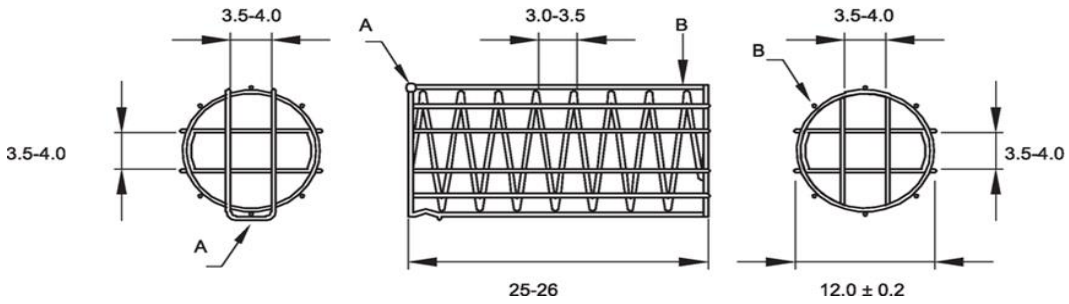


NOTE – 1. A and B dimensions do not vary more than 0.5 mm when part is rotated on center line axis.

2. Tolerances are ± 1.0 mm unless otherwise stated.

(Dimensions in mm)

Fig. 2.5.2-2: Paddle stirring element

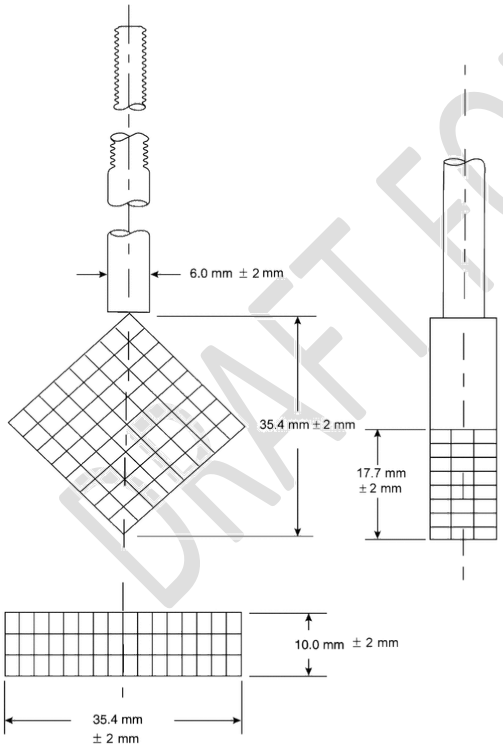


A. Acid-resistant wire clasp B. Acid-resistance wire support

(Dimensions in mm)

Fig. 2.5.2-~~3~~2a: Alternative sinker

♦An alternative to sinkers is the stationary basket. The dosage form is placed in a quadrangular basket made of stainless steel wire mesh, soldered in one of its upper, narrow sides and attached to the end of a stainless steel connecting rod (Fig. 2.5.2-~~4~~2b). The cover is placed in the horizontal diagonal of the basket. The rod assembly is attached to the cover of the dissolution vessel via an adjustable threaded steel rod, and is fixed by means of two Teflon nuts, about 3.2 cm from the center of the vessel, or by another appropriate means. The lower corner of the bottom of the basket is adjusted to about 1 cm above the top of the paddle blade (Fig. 2.5.2-~~5~~2c). The axis of the connecting rod is parallel to the axis of the paddle shaft along the vertical length of the connecting rod and the largest face of the basket lies in a vertical plane perpendicular to the radius of the cylinder of the vessel.

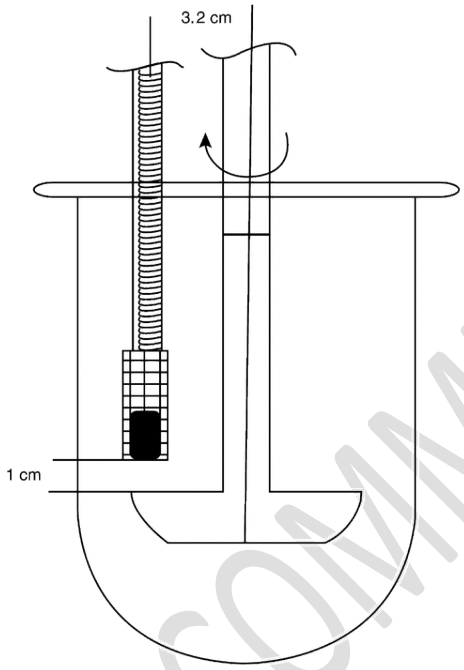


NOTE – 1. A and B dimensions do not vary more than 0.5 mm when part is rotated on center line axis.

2. Tolerances are ± 1.0 mm unless otherwise stated.

(Dimensions in mm)

Fig. 2.5.2-~~4~~2b: Stationary basket



(Dimensions in cm)

Fig. 2.5.2-~~5~~2c: Position of the stationary basket in the dissolution vessel.♦

Apparatus 3 (Reciprocating Cylinder)

~~The assembly consists of a set of cylindrical, flat-bottomed glass vessels, a set of glass reciprocating cylinders, inert fittings made from stainless steel, type 316 or equivalent or not react or interfere with the preparation under examination or the dissolution medium, screens (for eg. 20 mesh to 100 mesh) that are made of suitable non-absorbing and non-nonreactive material 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 set to maintain the dissolution medium at 36.5° to 37.5° 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 given in the individual monograph within ± 5 per cent. An apparatus that permits observation of the specimens 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 Fig. 2.5.2-5 unless otherwise specified in the individual monograph.~~

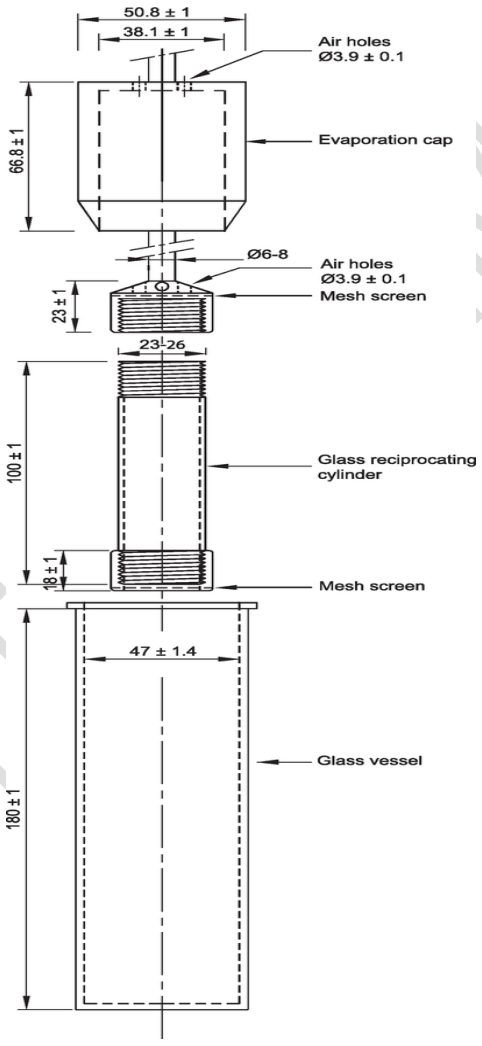
The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material) and screens that are made of suitable nonsorbing and nonreactive material and that are designed to fit the tops and 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 water-bath that permits maintaining the temperature of the dissolution medium inside the vessel at ~~37.0 ± 5°~~ 36.5° to 37.5° 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 per cent. 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 (Fig. 2.5.2-~~6~~3) unless otherwise specified.

♦**Dissolution medium**. Proceed as directed under Apparatus 1.

Time. Proceed as directed under Apparatus 1.

Filter suitability. Proceed as directed under Apparatus 1♦.



(Dimensions in mm)

Fig. 2.5.2-~~6~~3: Glass vessel and reciprocating cylinder

Apparatus 4 (Flow-Through Cell)

~~The assembly consists of a reservoir and a pump for the dissolution medium, a flow-through cell and a water bath set to maintain the dissolution medium at 36.5° to 37.5°. Use the specified cell type as given in the individual monograph. 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 which is ± 5 per~~

~~cent of the nominal flow rate, the flow profile is sinusoidal with a pulsation of 110 to 130 pulses per minute. A pump without pulsation may also be used. Dissolution test procedures using a flow-through cell must be characterized with respect to rate and any pulsation. The flow-through cell (see Fig. 2.5.2-6 and Fig. 2.5.2-7) 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 1mm diameter and with one bead of about 5 mm positioned at the apex to protect the fluid entry tube and a tablet holder (see Fig. 2.5.2-6 and Fig. 2.5.2-7) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath and the temperature is maintained at 36.5° to 37.5°.~~

The assembly consists of a reservoir and a pump for the dissolution medium; a flow-through cell; a water-bath or a heating device that maintains the dissolution medium at ~~37.0 ± 5°~~ 36.5° to 37.5° during the test.

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~~ 110 to 130 pulses per minute. Alternative pulsation rates and pumps without pulsation may also be used. The dissolution test procedure must specify the flow rate and the pulsation rate.

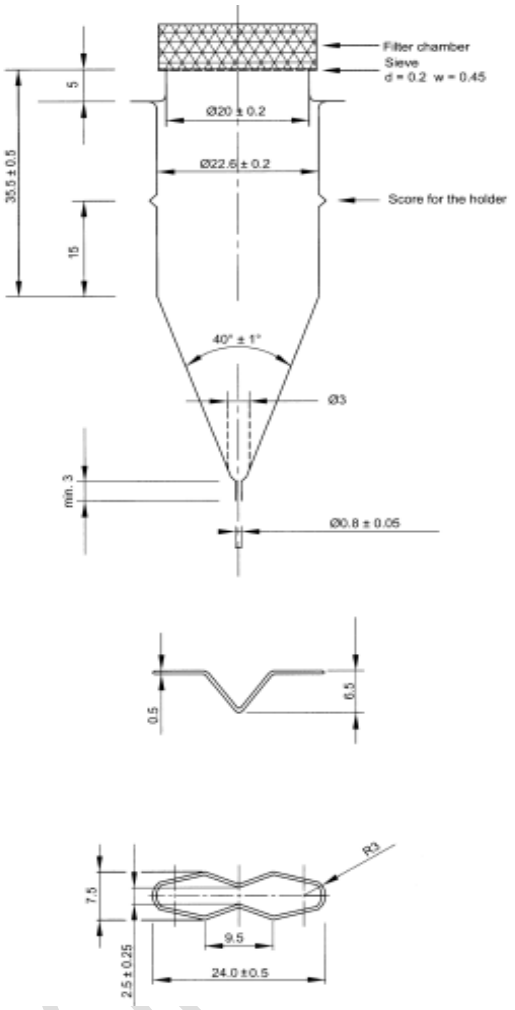
The flow-through cell (Fig. 2.5.2-~~7~~ 4 and 2.5.2-~~8~~5), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom 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~~tablet holder (Fig. 2.5.2-~~7~~ 4 and 2.5.2-~~8~~5), is available for positioning of the dosage unit, for example, inlay tablets. The temperature in the cell is maintained at ~~37.0 ± 5°~~ 36.5° to 37.5°.

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. Tube connections are as short as possible. Use suitably inert tubing, such as polytef, with about 1.6 mm inner diameter and inert flanged-end connections.

♦**Dissolution medium**. Proceed as directed under Apparatus 1.

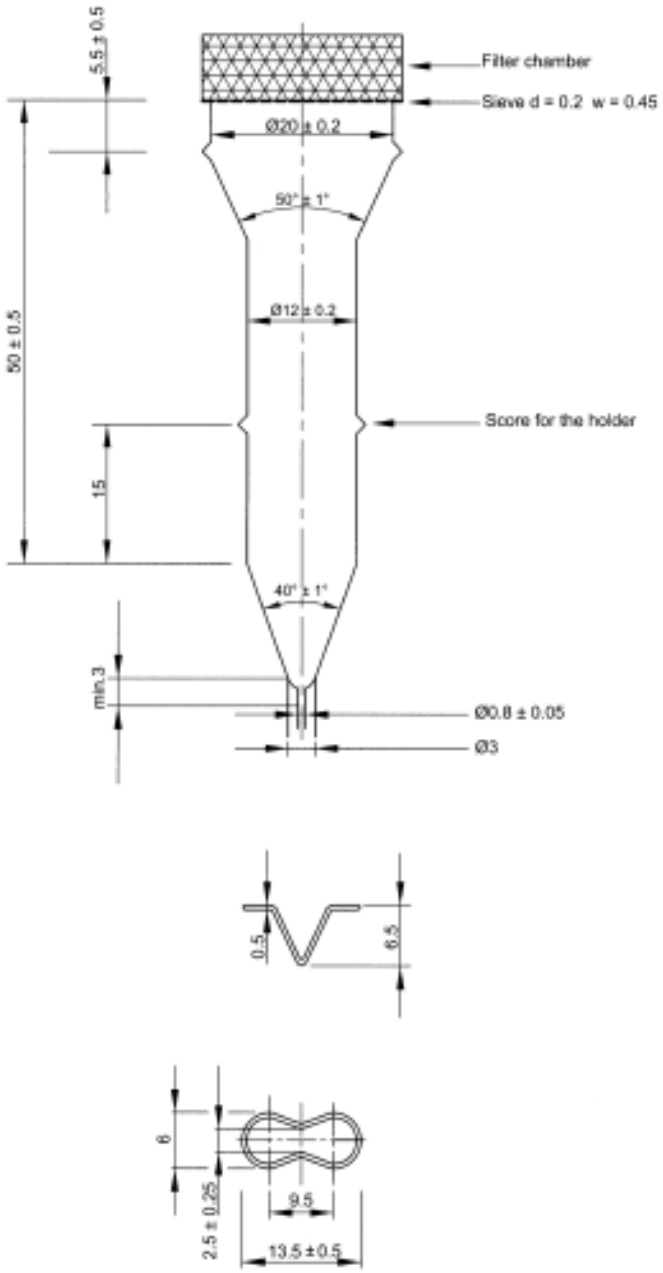
Time. Proceed as directed under Apparatus 1.

Filter suitability. Proceed as directed under Apparatus 1♦.



(Dimensions in mm)

Fig. 2.5.2-~~7~~4: Large cell for tablet, capsule and ♦suspension♦ (top), tablet holder for the large cell (bottom).



(Dimensions in mm)

Fig. 2.5.2-~~8~~5: Small cell for tablet, capsule and ♦suspension♦ (top), tablet holder for the small cell (bottom).

The apparatus can be operated in two different configurations:

Open configuration. The volume of the dissolution medium used is not fixed but is defined by the flow rate and the testing time. The dissolution medium is constantly pumped from the reservoir through the flow-through cell containing the dosage unit. The eluate is removed from the upper part of the flow-through cell and collected in a series of containers. The dissolution medium can be changed during a dissolution run. The concentration of active substance in the eluate in each collection container represents the mass fraction of active substance dissolved in the volume of the dissolution medium consumed over the collected time.

Closed-loop configuration. The volume of the dissolution medium is fixed. The dissolution medium is pumped from the reservoir through the flow-through cell containing the dosage unit. The eluate is returned to the reservoir; thus, completing the loop. The reservoir allows the medium to be stirred, heated, and sampled. The concentration of the active substance in the medium increases over time.

Apparatus qualification. 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), reciprocation rate (Apparatus 3), and flow rate of medium (Apparatus 4).

Determine the acceptable performance of the dissolution test assembly periodically.

Dissolution Medium

If the dissolution medium is a buffered solution, adjust the pH value of the solution to within 0.05 unit of the specified value, measured between 20° and 25°.

Dissolution medium for acid stage. ~~A~~ *0.1 M hydrochloric acid*.

Dissolution medium for buffer stage. 1 volume of 0.2 M tribasic sodium phosphate and 3 volumes of *0.1 M hydrochloric acid*. Adjust, if necessary, to pH 6.80 ± 0.05 with *2 M hydrochloric acid* or *2 M sodium hydroxide*.

The volume of dissolution medium specified is the volume within a tolerance of ±1 per cent measured between 20° and 25°.

If dissolved gases in the dissolution medium affect the results of the test, they must be reduced prior testing to a level that do not affect the results.

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.

Methods

For Apparatus 1 and Apparatus 2

~~***Conventional and prolonged-release solid dosage forms***~~

~~Place the stated volume of the dissolution medium, free from dissolved air, into the vessel of the apparatus. Assemble the apparatus and warm the dissolution medium to 36.5º to 37.5º. Unless otherwise stated, introduce individual dosage unit simultaneously and in a reproducible way in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit. When Apparatus 1 is used, place the tablet or capsule in a dry basket at the beginning of each test. Lower the basket into position before rotation. When Apparatus 2 is used, allow the tablet or capsule to sink to the bottom of the vessel prior to the rotation of the paddle. A suitable device such as a sinker made up of stainless steel, type 316 or any other inert material may be used to keep the dosage unit horizontal at the bottom of the vessel for tablets or capsules that would otherwise float or stick to the vessel.~~

~~Operate the apparatus immediately at the speed of rotation specified in the individual monograph. 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 blade or basket, not less than 10 mm from the wall of the vessel. Specimen withdrawal at each sampling time point should be from the same zone either manually or automatically.~~

~~Except in the case of single sampling, add a volume of dissolution medium equal to the volume of the samples withdrawn. After the specimen is withdrawn from the dissolution vessel, it may require additional processing like filtration, dilution, stirring and special storage conditions. Filter the sample solution through a frit filter (10 µm to 15 µm) followed by a membrane filter disc with an average pore diameter not greater than 1.0 µm (0.22 µm to 0.45 µm). Discard the first few ml of the filtrate. Perform the analysis as directed in the individual monograph. Repeat the whole operation five times. Where two or more tablets or capsules are directed to be placed together in the apparatus, carry out six replicate tests.~~

~~Application of direct insitu measurement technology like fibre optics into dissolution testing may also be useful in some cases. This technique requires appropriate validation.~~

~~For each of the tablet or capsule tested, calculate the amount of dissolved active ingredient in solution as a percentage of the stated amount where two or more tablets or capsules are placed together, determine for each test the amount of active ingredient in solution per tablet or capsules and calculate as a percentage of the stated amount.~~

~~Immediate~~♦ Conventional♦-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°~~ 36.5° to 37.5°, and remove the thermometer. When using Apparatus 1, place the dosage unit in the basket before immersion. When using Apparatus 2, drop the dosage unit into the vessel, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified stirring rate. At the testing time specified, or at each of the sampling times stated, withdraw an aliquot from a zone midway between the surface of the dissolution medium and the top of the rotating basket or paddle 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 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 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~~ ♦as directed in the individual monograph♦.

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.

Time. At each sampling time stated in the procedure within a tolerance of ±2 per cent withdraw aliquots. [3]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~~♦Prolonged♦-release dosage forms

Procedure. Proceed as described for ~~Immediate~~ ♦Conventional♦-Release Dosage Forms.

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

♦ For a pooled sample of conventional-release dosage forms

Use this method where method for a pooled sample is specified in the individual monograph. Method as directed for Conventional-release dosage forms in Apparatus 1 and Apparatus 2 in the Method section. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdraw, and use the pooled sample as the test specimen. Determine the average amount of the active ingredient dissolved in the pooled sample. ♦

~~Modified-release dosage forms~~

~~Gastro-resistant dosage forms Delayed~~♦Gastro♦-release dosage forms.

Procedure. Use Method A or Method B.

Method A

Acid stage. Place 750 ml of dissolution medium for Acid Stage in the vessel and assemble the apparatus. Allow the medium in the vessel to equilibrate to a temperature of ~~37.0 ± 0.5°~~ 36.5° to 37.5°. Place ~~1~~ one dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified stirring rate. After 2 hours of operation, 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.~~ ♦as directed in the individual monograph♦.

Buffer stage. [NOTE—Complete the operations of adding the buffer solution and adjusting the pH within 5 minutes.] With the apparatus operating at the stirring rate specified, add to the fluid in the vessel 250 ml of 0.2 M tribasic sodium phosphate that has been equilibrated to ~~37.0 ± 0.5°~~ 36.5° to 37.5°. Adjust, if necessary, with *2 M hydrochloric acid* or *2 M 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 testing time specified, withdraw an aliquot of the fluid, and perform the analysis ~~using a suitable assay method.~~ ♦as directed in the individual monograph♦.

[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.

Method B

~~*Acid stage*. Place 1000 ml of 0.1M hydrochloric acid in the vessel and assemble the apparatus. Warm the dissolution medium to 36.5º to 37.5º. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in the acid medium, withdraw an aliquot of the liquid and proceed immediately as directed under Buffer stage. Perform the analysis of the aliquot using a suitable assay method.~~

~~*Buffer stage*. Use buffer that has previously been warmed to 36.5º to 37.5º. Drain the acid from the vessel and add 1000 ml of pH 6.8 phosphate buffer, prepared by mixing 3 volumes of 0.1M hydrochloric acid with 1 volume of 0.2M solution of trisodium phosphate dodecahydrateand adjust, if necessary, with 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8 ± 0.05. This may also be done 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 minutes, or for the specified time. At the end of this period, withdraw an aliquot of the liquid and perform the analysis using a suitable assay method. The test may be concluded in a shorter time period than that specified for the Buffer Stage if the requirement for the minimum amount dissolved is met at an earlier time.~~

Acid Stage. Place 1000 ml of dissolution medium for Acid Stage in the vessel and assemble the apparatus. Allow the medium in the vessel to equilibrate to a temperature of ~~37.0 ± 0.5º~~ 36.5° to 37.5°. Place ~~1~~ one dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified stirring rate. After 2 hours of operation, 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.~~ ♦as directed in the individual monograph♦.

Buffer stage. [NOTE—For this stage of the procedure, use buffer solution that previously has been equilibrated to a temperature of ~~37.0 ± 0.5º~~ 36.5° to 37.5°*.]* Drain the medium from the vessel and add to the vessel 1000 ml of dissolution medium for Buffer Stage. *[NOTE—This may be accomplished also by removing from the apparatus the vessel containing the Acid Stage medium and replacing it with another vessel containing the dissolution medium for Buffer Stage and transferring the dosage unit to the vessel containing the dissolution medium for Buffer Stage.]*

Continue to operate the apparatus for 45 minutes, or for the specified testing time. At the end of the time specified withdraw an aliquot of the fluid and perform the analysis ~~using a suitable assay method~~ ♦as directed in the individual monograph♦.

Time. All sampling times stated are to be observed within a tolerance of ±2 per cent, unless otherwise specified[4].

[4]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.

For Apparatus 3

~~***Conventional and prolonged-release dosage forms***~~

~~Place the stated volume of the dissolution medium in each vessel of the apparatus. Assemble the apparatus, and warm the dissolution medium to 36.5° to 37.5°. Place one dosage unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 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 solution under test from a zone midway between the surface of the dissolution medium and the bottom of each vessel~~

~~***Immediate*** ♦***Conventional***♦***-release dosage forms***

Procedure. A dissolution test can be conducted either in a single vessel or in multiple consecutive vessels by moving the reciprocating cylinder from vessel to vessel. Place the stated volume of the dissolution medium in each vessel, assemble the apparatus, equilibrate the dissolution medium to ~~37.0 ± 0.5°~~ 36.5° to 37.5°, and remove the thermometer. Place ~~1~~ one dosage unit the reciprocating cylinder then place it in the dissolution medium, taking care to minimize the formation of air bubbles on the surface of the dosage unit, immediately operate the apparatus as specified. Keep the vessel covered with the evaporation cap for the duration of the test.

Single vessel operation. At each of the sampling times, raise the reciprocating cylinders and withdraw an aliquot of the solution under test from a zone midway between its surface and the bottom of each vessel. Replace the aliquot withdrawn for the analysis with an equal volume of fresh dissolution medium at 37° or when it can be shown that this compensation is not necessary, correct for the volume change in the calculation. Resume the test when the procedure involves multiple sampling times. Perform the analysis ~~using a suitable assay method~~♦ as directed in the individual monograph♦.

Multiple vessel operation. At each of the sampling times, transfer the reciprocating cylinder to the next vessel and immediately withdraw an aliquot from the previous vessel. Perform the analysis ~~using a suitable assay method~~ ♦as directed in the individual monograph♦.

Time. At each sampling time stated in the procedure within a tolerance of ±2 per cent withdraw aliquots.

~~Extended~~ ♦Prolonged♦-release dosage forms

Procedure. Proceed as described for ~~Immediate~~♦Conventional♦-Release Dosage Forms under Apparatus 3.

Time. The sampling times (generally three), are expressed in hours.

~~Modified-release dosage forms~~

~~Gastro-resistant dosage forms.~~ ~~Use method A or Method B.~~

~~Proceed as directed for modified-release dosage forms, Method B under Apparatus 1 and Apparatus 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 250 ml unless otherwise specified in the individual monograph.~~

~~Delayed~~♦Gastro♦-release dosage forms

Procedure

Multiple vessel operation. Fill the first vessel with the dissolution medium for Acid Stage and fill the next vessel with the dissolution medium for Buffer Stage using the volume specified in the procedure.

Time. Unless otherwise specified, withdraw aliquots of Acid Stage medium at 2 hours and of Buffer Stage medium at 45 minutes. Observe all sampling times within a tolerance of ± 2 per cent.

For Apparatus 4

~~Conventional and prolonged-release dosage forms~~

~~Place the glass beads into the cell specified in the monograph. Place one dosage unit on top of the beads or if specified in the monograph on a dosage holder. 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 36.5° to 37.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5 per cent. Collect the eluate by fractions at each of the times stated. Apparatus 4 can be operated in open loop and closed loop mode.~~

~~Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage units.~~

~~Immediate~~♦Conventional♦-release dosage forms

Procedure. Place the glass beads into the specified cell. Place~~1~~ one dosage unit on top of the beads or, if specified, in a dosage form holder (see Fig. 2.5.2-~~5~~ 4 and 2.5.2-~~6~~5). Assemble the filter head and fix the parts together by means of a suitable clamping device. Using the pump introduce the dissolution medium warmed to ~~37.0 ± 0.5°~~ 36.5° to 37.5° through the bottom of the cell to obtain the flow rate specified. Operate the apparatus in one of the two configurations. Perform the analysis ~~using a suitable assay method~~ ♦as directed in the individual monograph♦.

Time. At each sampling time stated in the procedure within a tolerance of ±2 per cent withdraw aliquots.

~~*Extended*~~♦*Prolonged*♦***-release dosage forms***

Procedure. Proceed as described for ~~Immediate~~♦Conventional♦-Release Dosage Forms under Apparatus 4.

Time. The sampling times (generally three), are expressed in hours.

~~***Modified release dosage forms***~~

~~***Gastro-resistant dosage forms.*** Use method A or Method B.~~

~~Proceed as directed for modified-release dosage forms under Apparatus 1 and Apparatus 2, using the specified media~~

~~*Delayed*~~♦*Gastro*♦***-release dosage forms***

Procedure

Proceed as described for ~~Immediate~~♦Conventional♦-Release Dosage Forms under Apparatus 4. Use first the dissolution medium for Acid Stage and then the dissolution medium for Buffer Stage. To change the dissolution medium, stop the pump, replace the dissolution medium reservoir and resume the test.

Time. Unless otherwise specified, withdraw aliquots of Acid Stage medium at 2 hours and Buffer Stage medium at 45 minutes within a tolerance of ± 2 per cent.

~~**Acceptance criteria for different dosage forms**~~

~~***Conventional-release dosage forms***~~

~~Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units conform to Table 1. If the results do not conform to the requirements at stage S_1 given in the table, continue testing with additional dosage units through stages S_2 and S_3 unless the results conform at stage S_2.~~

~~Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of the dissolution medium. Perform the analysis as directed in the individual monograph. Make any necessary correction.~~

~~Correction factors should not be greater than 25 per cent of the stated amount.~~

~~Table 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 unit is less than Q − 25 per cent**.~~

~~*Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labelled content.~~

~~**Percentages of the labelled content.~~

Interpretation

~~***Immediate***~~♦*Conventional*♦***-release dosage forms***

Unless otherwise specified, the requirements of the test are met if the quantities of active ingredient dissolved comply with ~~Acceptance~~ Table 1. Continue testing through the three stages unless the results comply at either S_1 or S_2. The quantity, Q, is the specified amount of active ingredient expected to dissolved within the time specified in the procedure, expressed as a percentage of the labeled content; similarly the 5 per cent, 15 per cent, and 25 per cent values in the ~~Acceptance~~ Table 1 are expressed as percentages of the labeled content.

Table 1

Level	Number of dosage units tested	Acceptance criteria
S_1	6	No individual value is less than Q* + 5 per cent**.
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 per cent**.
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 per cent** and no value is less than Q – 25 per cent**.

♦*Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labelled content.

**Percentages of the labelled content. ♦

♦Conventional -release dosage forms pooled sample

Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the pooled sample conform to Table ~~2~~1-A. If the results do not conform to the requirement at stage S_1 given in the table, continue testing with additional dosage units through stages S_2 and S_3 unless the results conform at stage S_2.

Table ~~2~~1-A

Level	Number of dosage units tested	Acceptance criteria
S1	6	Average amount dissolved is ~~NLT~~ not less than Q +10 per cent.
S2	6	Average amount dissolved (S1+ S2) is ~~NLT~~ not less than Q +5 per cent.
S3	12	Average amount dissolved (S1+ S2+ S3) is ~~NLT~~ not less than Q.

♦

~~***Prolonged-release dosage forms***~~

~~Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units conform to Table 2. If the results do not conform to the requirements at stage L_1 given in the table, continue testing with additional dosage units through stages L_2 and L_3 unless the results conform at stage L_2.~~

~~The limits embrace each value of Q, the amount dissolved at each specified dosing interval. Where more than one range is specified, the acceptance criteria apply to each range.~~

~~Table 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 amount 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.~~

~~Extended~~♦Prolonged♦-release dosage forms

Unless otherwise specified, the requirements of the test are met if the quantities of active ingredient dissolved comply with ~~Acceptance~~ Table ~~3~~2. Continue testing through the three levels unless the results comply at either L_1 or L_2. Limits for the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits encompass each value of the amount dissolved at each sampling time. Where more than one range is specified, the acceptance criteria apply individually to each range.

Table ~~3~~2

Level	Number of dosage units 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 value 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 and more than 20 per cent of labelled content below the stated amount at the final test time.

~~Modified-release dosage forms~~

~~*Acid stage*. Unless otherwise specified, the requirements of this part 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 3. Continue the testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level.~~

~~Table 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 of this part 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 4. Continue the testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level. The value of Q in Table 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.~~

~~Table 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 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*.~~

~~Delayed~~ ♦ Gastro ♦ -release dosage forms

Acid stage. Unless otherwise specified, the requirements of this portion of the test are met if based on the percentage of the labeled content, the quantities, of active ingredient dissolved comply with ~~Acceptance~~ Table ~~4~~ 3. Continue testing through all levels unless the results of both Acid Stage and Buffer Stages comply at an earlier level.

Table ~~4~~ 3

Level	Number of dosage units 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 of the test are met if the quantities of active ingredient dissolved comply with ~~Acceptance~~ Table ~~5~~ 4. Continue testing through the three levels unless the results of both stages comply at an earlier level. The value of Q in ~~Acceptance~~ Table ~~5~~ 4 is 75 per cent dissolved unless otherwise specified. The quantity, Q, is the total amount of active ingredient expected to dissolve in both stages, expressed as a percentage of the labeled content. Similarly, the 5 per cent and 15 per cent values in ~~Acceptance~~ Table ~~5~~ 4 are expressed as percentages of the labeled content.

Table ~~5~~ 4

Level	Number of dosage units tested	Acceptance criteria
B_1	6	No individual 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 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.

♦**Performance verification test, Apparatus 1 and Apparatus 2**. The suitability for the individual apparatus is demonstrated by the performance verification test using *prednisone tablet IPRS* periodically, according to the operating conditions specified in the technical data sheet. The apparatus is suitable if the results obtained are within the acceptance range stated in the technical data sheet specific to the lot of *prednisone tablet IPRS* used. ♦