Figure 5. Apparatus 4, small cell for tablets and capsules (top), tablet holder for the small cell (bottom). (All measurements are expressed in mm unless noted otherwise.)

The apparatus uses a clamp mechanism and two O-rings to assemble the cell. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections.

APPARATUS SUITABILITY

The determination of suitability of a test assembly to perform dissolution testing must include conformance to the dimensions and tolerances of the apparatus as given above. In addition, critical test parameters that have to be monitored periodically during use include volume and temperature of the *Dissolution Medium,* rotation speed *(Apparatus 1* and *Apparatus 2),* dip rate *(Apparatus 3),* and flow rate of medium *(Apparatus 4).*

Determine the acceptable performance of the dissolution test assembly periodically. ✦The suitability for the individual apparatus is demonstrated by the *Performance Verification Test.*

Performance Verification Test, Apparatus 1 and 2— Test *USP Prednisone Tablets RS* according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the technical data sheet specific to the lot used and the apparatus tested.

Performance Verification Test, Apparatus 3— Test USP Chlorpheniramine Maleate Extended-Release Tablets RS according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the technical data sheet specific to the lot used.

Performance Verification Test, Apparatus 4— [To come.]✦

PROCEDURE

Apparatus 1 and Apparatus 2

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the specified apparatus ✦given in the individual monograph✦, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate ✦given 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 basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple

sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 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 mixture under test at suitable times.] Perform the analysis ✦as directed in the individual monograph✦ using a suitable assay method.[3] Repeat the test with additional dosage form 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 standard apparatus described in this general chapter is necessary.

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

Time— 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. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

✦**Procedure for a Pooled Sample for Immediate-Release Dosage Forms** —Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed in *Procedure* for *Apparatus 1 and Apparatus 2* in *Immediate-Release Dosage Forms.* Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test specimen. Determine the average amount of the active ingredient dissolved in the pooled sample.✦

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms.*

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

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

DELAYED-RELEASE DOSAGE FORMS NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

Use *Method A* or *Method B* and the apparatus specified ✦in the individual monograph✦. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A—

Procedure ✦(unless otherwise directed in the individual monograph)✦ —

ACID STAGE— Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate ♦given in the monograph♦.

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

Perform an analysis of the aliquot using a suitable assay method. ♦The procedure is specified in the individual monograph.♦

BUFFER STAGE— [NOTE—Complete the operations of adding the buffer and adjusting the pH within 5 minutes.]

With the apparatus operating at the rate specified ♦in the monograph♦, add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time ♦given in the individual monograph♦. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ♦The procedure is specified in the individual monograph. 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.♦

Method B—

Procedure ♦(unless otherwise directed in the individual monograph)♦ —

ACID STAGE— Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified ♦in the monograph♦. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ♦The procedure is specified in the individual monograph.♦

BUFFER STAGE— [NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—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 minutes, or for the specified time ♦given in the individual monograph♦. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ♦The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.♦

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form 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. Perform the analysis as directed ♦in the individual monograph♦. If necessary, repeat the test with additional dosage-form units.

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

Time —Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2.*

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 3.*

Dissolution Medium —Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2.*

Time —Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as described for *Delayed-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 300 mL).

Time —Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2.*

Apparatus 4 (Flow-Through Cell)

IMMEDIATE-RELEASE DOSAGE FORMS

Place the glass beads into the cell specified ♦in the monograph♦. Place 1 dosage unit on top of the beads or, if specified ♦in the monograph♦, 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° through the bottom of the cell to obtain the flow rate specified ♦in the individual monograph♦ and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed ♦in the individual monograph♦. Repeat the test with additional dosage-form units.

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

Time —Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2.*

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

Dissolution Medium —Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

Time —Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2,* using the specified media.

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

INTERPRETATION

Immediate-Release Dosage Forms

Unless otherwise specified ♦in the individual monograph♦, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 1.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient ♦specified in the individual

monograph ◆, expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in *Acceptance Table 1* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
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%.
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%, and no unit is less than Q − 25%.

◆**Immediate-Release Dosage Forms Pooled Sample—** Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

◆

Extended-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph ◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified ◆in the individual monograph ◆, the acceptance criteria apply individually to each range.

Acceptance Table 2

Level	Number Tested	Criteria

L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 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% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 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% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Delayed-Release Dosage Forms

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA.

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

Acceptance Table 3

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

Buffer Stage— Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 4*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 4* is 75% dissolved unless otherwise specified ◆in the individual monograph◆. The quantity, Q ◆specified in the individual monograph◆ is the total amount of active ingredient dissolved in both the *Acid* and *Buffer Stages*, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in *Acceptance Table 4* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units (B_1 + B_2) is equal to or greater than Q, and no unit is less than Q – 15%.
B_3	12	Average 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%, and no unit is less than Q – 25%.

---

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

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

[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 ingredient or contain extractable substances that would interfere with the analysis.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, 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.

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

Topic/Question	Contact	Expert Committee
General Chapter	William E. Brown Senior Scientific Liaison 1-301-816-8380	(GCDF2010) General Chapters - Dosage Forms
Reference Standards	RS Technical Services 1-301-816-8129 rstech@usp.org	

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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.

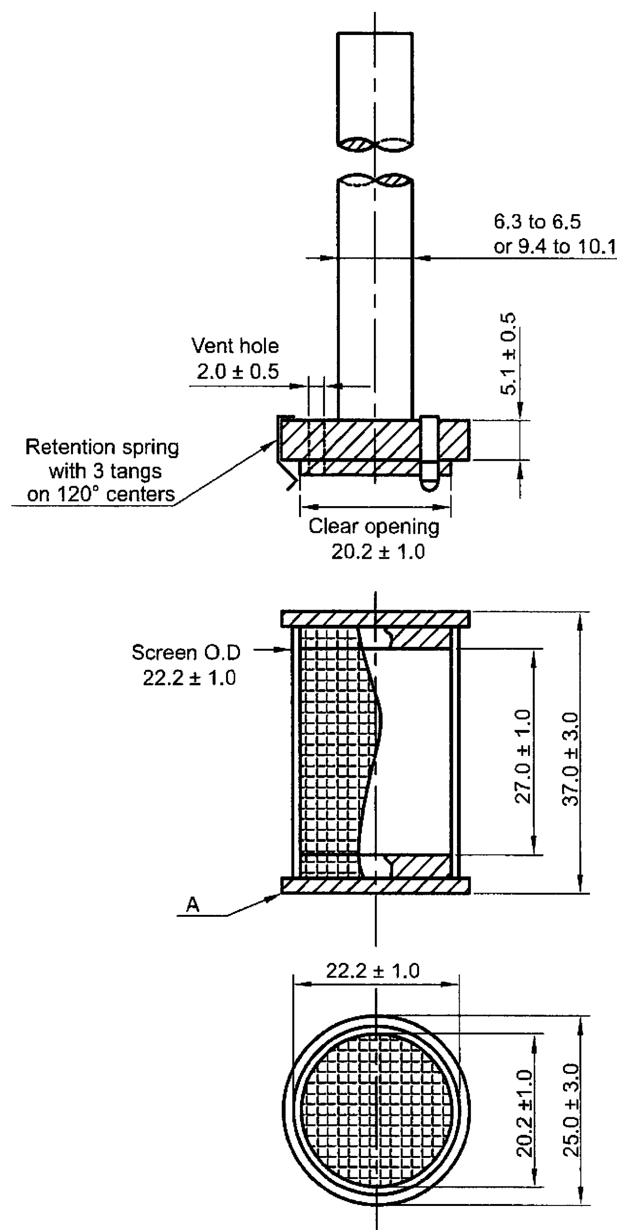
APPARATUS

Apparatus 1 (Basket apparatus). The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material[6]; 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[7]. 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.

A basket having a gold coating of about 2.5 μm (0.0001 inch) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

Apparatus 2 (Paddle apparatus). Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel, at any point, and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2.9.3.-2. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 2.9.3.-3. Other validated sinker devices may be used.



1) Screen with welded seam: 0.25-0.31 mm wire diameter with wire opening of 0.36-0.44 mm. After welding the screen may be slighty altered.

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

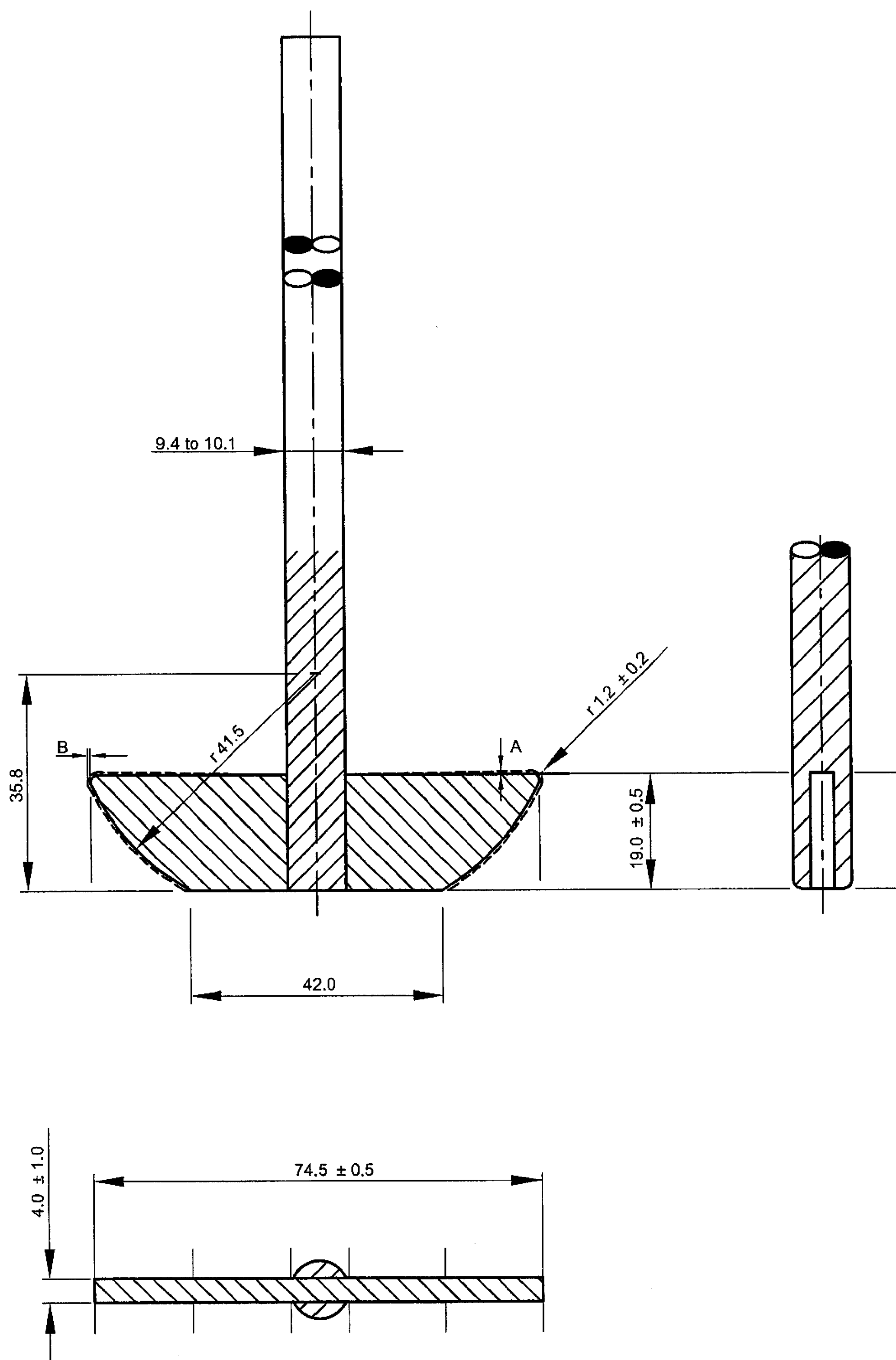
Figure 2.9.3.-1. – *Apparatus 1, Basket stirring element*

Dimensions in millimetres

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,

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

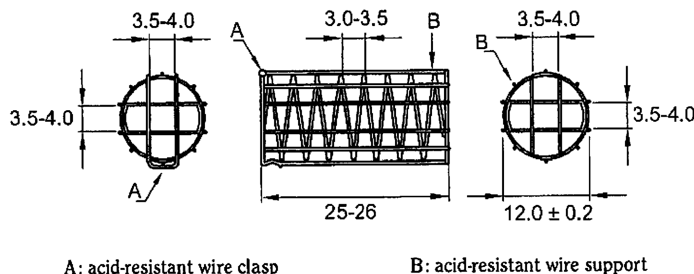
(7) If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of samples.



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

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.



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

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

Apparatus 4 (Flow-through cell). The assembly consists of a reservoir and a pump for the dissolution medium; a flow-through cell; a water-bath that maintains the dissolution medium at 37 ± 0.5 °C. Use the specified cell size.

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

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

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

Determine the acceptable performance of the dissolution test assembly periodically.

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(8). 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(9).

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.

(8) 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.
(9) 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.

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.

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.

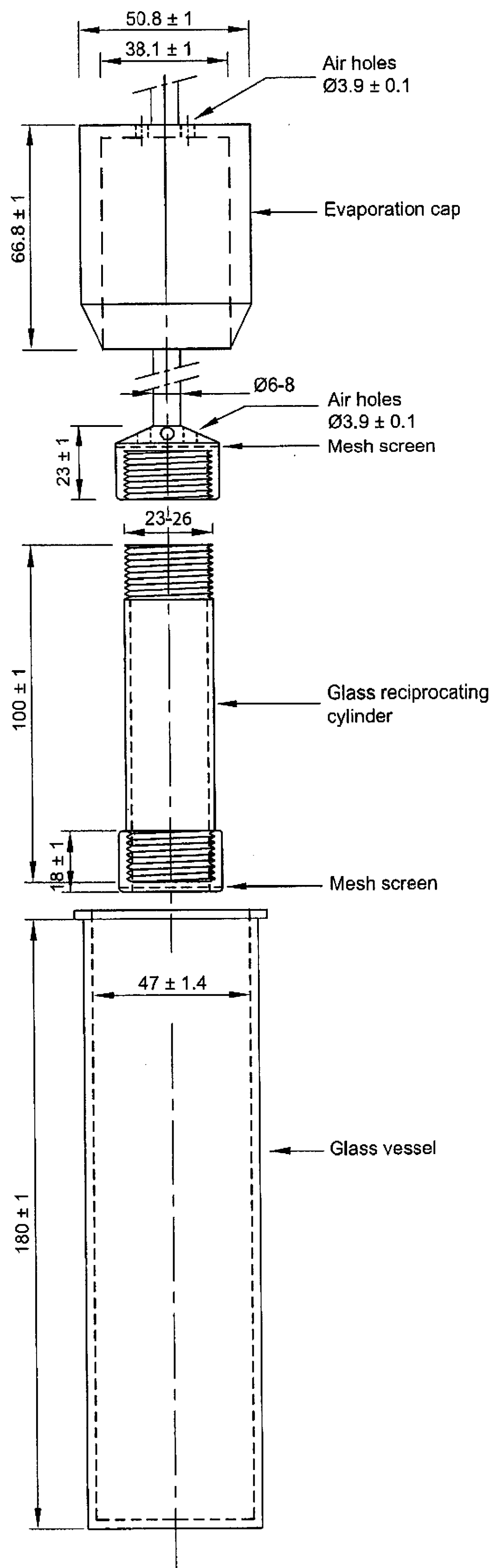


Figure 2.9.3.-4. – *Apparatus 3, glass vessel and reciprocating cylinder*

Dimensions in millimetres unless otherwise specified

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.

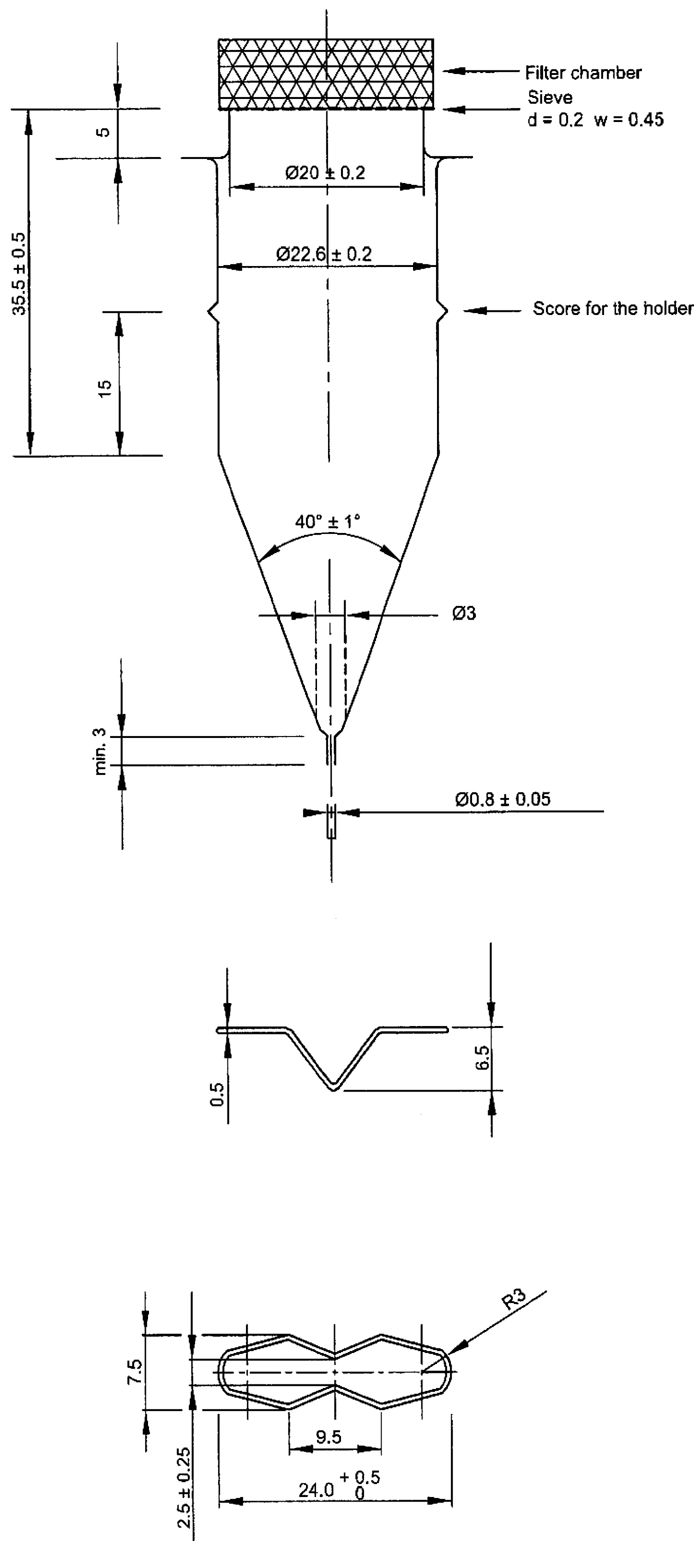


Figure 2.9.3.-5. – *Apparatus 4, large cell for tablets and capsules (top), tablet holder for the large cell (bottom)*
Dimensions in millimetres unless otherwise specified

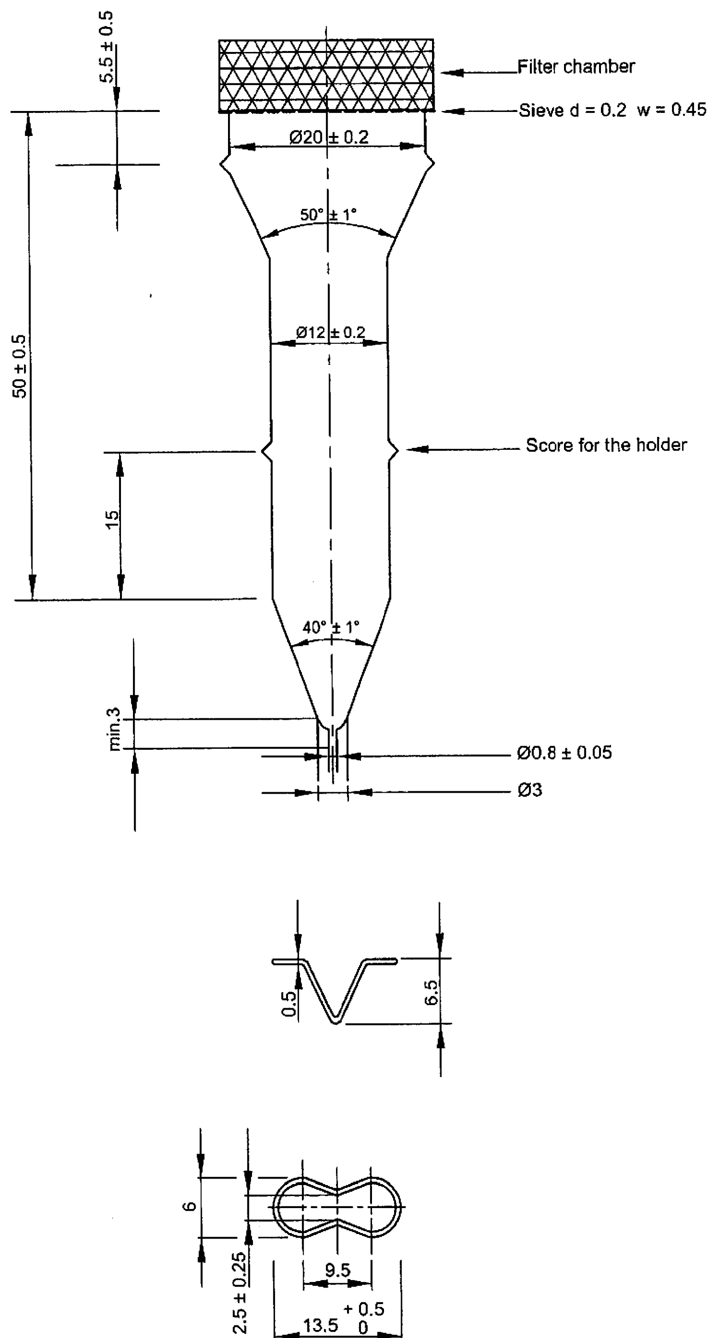


Figure 2.9.3.-6. – *Apparatus 4, small cell for tablets and capsules (top), tablet holder for the small cell (bottom)*
Dimensions in millimetres unless otherwise specified

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.

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 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.*

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

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.

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.

01/2010:20907

2.9.7. FRIABILITY OF UNCOATED TABLETS(10)

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet breaking force.

Use a drum, with an internal diameter between 283-291 mm and a depth between 36-40 mm, of transparent synthetic polymer with polished internal surfaces, and subject to minimum static build-up (see Figure 2.9.7.-1.). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5-85.5 mm that extends from the middle of the drum to the outer wall. The outer diameter of the central ring is between 24.5-25.5 mm. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

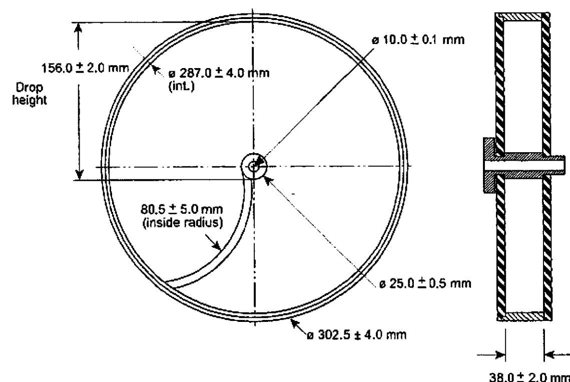


Figure 2.9.7.-1. — *Tablet friability apparatus*

For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test is repeated twice and the mean of the 3 tests determined. A maximum loss of mass (obtained from a single test or from the mean of 3 tests) not greater than 1.0 per cent is considered acceptable for most products.

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. In the case of hygroscopic tablets, a humidity-controlled environment is required for testing.

A drum with dual scooping projections, or apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.

01/2010:20926

2.9.26. SPECIFIC SURFACE AREA BY GAS ADSORPTION(11)

INTRODUCTION

The specific surface area of a powder is determined by physical adsorption of a gas on the surface of the solid and by calculating the amount of adsorbate gas corresponding to a monomolecular layer on the surface. Physical adsorption results from relatively weak forces (van der Waals forces) between the adsorbate gas molecules and the adsorbent surface of the test powder. The determination is usually carried out at the temperature of liquid nitrogen. The amount of gas adsorbed can be measured by a volumetric or continuous flow procedure.

BRUNAUER, EMMETT AND TELLER (BET) THEORY AND SPECIFIC SURFACE AREA DETERMINATION

MULTI-POINT MEASUREMENT

The data are treated according to the Brunauer, Emmett and Teller (BET) adsorption isotherm equation:

$$\frac{1}{\left[V_a\left(\frac{P_o}{P}-1\right)\right]}=\frac{C-1}{V_mC}\times\frac{P}{P_o}+\frac{1}{V_mC} \qquad (1)$$

P = partial vapour pressure of adsorbate gas in equilibrium with the surface at 77.4 K (b.p. of liquid nitrogen), in pascals,

P_o = saturated pressure of adsorbate gas, in pascals,

V_a = volume of gas adsorbed at standard temperature and pressure (STP) [273.15 K and atmospheric pressure (1.013×10^5 Pa)], in millilitres,

V_m = volume of gas adsorbed at STP to produce an apparent monolayer on the sample surface, in millilitres,

C = dimensionless constant that is related to the enthalpy of adsorption of the adsorbate gas on the powder sample.

A value of V_a is measured at each of not less than 3 values of P/P_o.

(10) This chapter has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation (9.19)*.
(11) This chapter has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation (9.20)*.

２２年度　厚生労働科学研究費補助金　分担研究報告書

国際調和された医薬品品質システムの導入・実践の国際調和に関する研究

研究分担者　国立医薬品食品衛生研究所薬品部第三室長　檜山　行雄

本分担研究21年度に引き続きではＩＣＨ（医薬品規制国際調和会議）によるQ8（製剤開発)、Q9（品質リスクマネジメント）及びQ10（医薬品品質システム）の３つのガイドラインの実施作業部会（Implementation Working Group：Q-IWG）の活動について報告する。

Q-IWGの活動目的は、Q8、Q9及びQ10の一貫した導入と実践を世界的に行うこと、及び、三つのガイドラインの相乗効果により大きな成果を上げることにある。導入・実践に関しては今後注意深く、精密に作業を行っていかなければならないという認識のもと，2007年に、非公式Q-IWGが開催され、2010年11月の福岡会議までに７回のQ-IWG作業部会会議が行われた。

検討課題としては、研究開発から生産までのライフサイクルを対象に、用語の共通理解、三つのガイドラインの相互関係の理解を進めること、申請資料の中にどの様に書き込むのかといった調和の程度も課題として取り上げる。又、Q8、Q9及びQ10の導入・実践による、既存のICHのQualityガイドラインへの影響の評価を行う。さらに、コミュニケーションとトレーニングを、Q&Aや教育資料の作成を通じ行う。

具体的な活動として、2010年11月までに46のQ&Aを発行した。「Q：商業生産スケールにおけるプロセスバリデーションの検討中に、デザインスペースのouter limitsでの検討が必要か？A：不要である。商業生産スケールにおけるプロセスバリデーションの検討中に、デザインスペースのouter limitsで、適格性確認のバッチ生産を行う必要はない。デザインスペースは開発段階で十分に検討されていなければならない。」というQ&Aが今年新たに採択された。2010年、6月にはエストニアのタリン市、10月初旬にはアメリカのワシントンDC、10月下旬には東京で３日間に渡る研修会を実施した。

今後の活動：上記研修会の参加者から寄せられた160に上る質問・要望を11月のQIWG福岡会議において精査した。その結果、今後６つのサブテーマについてpoints to considerを作成することとなった。それらは、管理戦略（control strategy），Critical / Non-critical, 申請資料の程度（内容と量）, QbD下におけるモデル化の役割，デザインスペース，プロセスバリデーション / プロセスベリフィケーションであり、緊急度の高い前３者を2011年6月のQIWGシンシナチ会議において完成させ、残りの３つについては2011年11月QIWG欧州会議において完成させることとなった。

研修会を通じ、ガイドラインの作成に直接関与した者（ICHの専門家）とそれ以外の専門家の間では、多くの点で、基本的な理解の差があること、又、ICHの専門家内でも認識が統一されていない点が明らかになったことは意義のあることであった。Q-IWGにおける、Q&A及び教育資料作成を通じ、技術面のみならず行政面においても相乗的な国際調和の進展が期待される。

A　はじめに

21 年度に引き続き、ＩＣＨ（医薬品規制国際調和会議：参考１）による Q8（製剤開発)、Q9（品質リスクマネジメント）及び Q10（医薬品品質システム）の３つのガイドラインの実施作業部会（Implementation Working Group : Q-IWG）の活動について報告する。

Q-IWG の活動目的は、Q8、Q9 及び Q10 の一貫した導入と実践を世界的に行うこと、及び三つのガイドラインの相乗効果によって、より大きい成果を上げることにある。2003 年の ICHGMP ワークショップにおいて合意されたビジョン（参考２）に基づき、製剤開発(Q8)、品質リスクマネジメント(Q9)、医薬品品質システム(Q10)が作成された。これらのガイドラインは、概念的であり、今後の方針に関わることが多く、またなじみのない概念も含まれている。2006 年の Quality Strategy Meeting では、Q8、Q9 及び Q10 の導入・実践に関しては今後注意深く、ある程度精密に作業を行っていかなければ ICH ビジョンの実現は難しいという認識がされ, 2007 年になり、非公式の Q-IWG が開催された。

その後、2011 年 11 月の福岡会議までに以下のように７回の Q-IWG 作業部会会議が行われた。

2007 年 11 月　非公式会議（横浜）
2008 年 6 月　ポートランド会議
2008 年 11 月　ブラッセル会議
2009 年 6 月　横浜会議
2009 年 10 月　セントルイス会議
2010 年 3 月　中間会議（パリ）
2010 年 6 月　タリン会議（エストニア）
2010 年 11 月　福岡会議

Q-IWG の検討課題と運営

検討課題としては、研究開発から生産までのライフサイクルを対象に、用語の共通理解、Q8、Q9 及び Q10 のガイドラインの相互関係の理解を進めること、また、申請資料の中にどの様に書き込むのかといった調和の程度も課題として取り上げる。Q8、Q9 及び Q10 の導入・実践を行った場合に、今まで作成された ICH の Quality ガイドラインに影響が及ぶことが考えられるので、それらの課題を洗い出して対応していく。　さらに、Q8、Q9 及び Q10 ガイドラインに関するコミュニケーションとトレーニングを、Q&A や教育資料の作成を通じおこなう。外部団体と共同作業も行う。

Q-IWG の活動として、Quality by Design、知識管理、医薬品品質システム・査察の三つの領域についてどのような具体的な問題があるのかを洗い出す。IWG の成果物である、Q&A、White papers、Position papers や事例の作成、ワークショップの開催をする。さらに、ICH の web site を通して提案を受け付ける。

B　昨 21 年度の成果

2009 年 6 月の横浜会議ではＱ＆Ａの作成、Case study のレビュー、教育プログラムの構築の三つの領域で議論が行われた。10 件の Q&A が新たに採択された。外部論文を review して引用するには、多くの労力が必要となるためこれを断念した。それに代わり、IWG 自身が外部団体と共同で Position Papers や White Papers を書くことになり、Task force を作り、今後取り組むこととなった。2010 年欧州、米国、日本で開催された教育研修会の骨格が決められた。

2009 年 10 月のセントルイス会議では、プロセスバリデーションに関して調整を図り、Q&A 1.1.2 として合意した。トレーニングに用いる教育資料として厚生労働科学研究班の成果『サクラ錠』の事例が開発シナリオとして採用されることが決まり、これを基に生産シナリオ、審査シナリオ、査察シナリオが作成されることとなった。

2010 年 3 月パリ中間会議では、6 月にタリ