a soft residue or a muddy substance remains in the glass tube.

(3) Pills—Apply the test for tablets. However, the test is performed with the 1st fluid for 60 minutes. If a residue is observed in a glass tube, the test should be continued for 60 minutes with the 2nd fluid.

(4) Capsules—Carry out the test using water as the test fluid. Observe the capsules after 20 minutes of operation with auxiliary disks: the capsules comply with the test, if no residue of the capsules or only the film of the capsules, or only a small amount of soft residue or a muddy substance remains in the glass tube. If only one capsule remains intact or shows no evidence of leakage of its content even though the film is dissolved, ruptured or ripped off, repeat the test on 6 additional capsules; the capsules comply with the test, if no residue or only the film of the capsules or a small amount of soft residue or a muddy substance remains in the glass tube.

(5) Granules—Shake granules on a No.30 (500 μm) sieve as directed in (1) Granules under the Particle Size Distribution Test for Preparations, transfer 0.10 g of the residue on the sieve to each of the 6 auxiliary tubes, secure the 6 tubes to the bottom of the basket tightly, and carry out the test using water as the test fluid, unless otherwise specified. Observe the granules after 30 minutes of operation: the granules comply with the test, if no residue remains in any of the auxiliary tubes or only one sample remains intact in only one auxiliary tube, or if the residue is the film of the granules or only a small amount of a soft residue or a muddy substance is present. In case of coated granules, apply the test with water, and operate for 60 minutes.

(6) Enteric coated preparations

(i) Enteric coated preparations other than those falling under (ii)

Perform the following two tests, (a) the test with the 1st fluid and (b) the test with the 2nd fluid.

(a) The test with the 1st fluid

Carry out the test using the 1st fluid as the test fluid. Observe the sample after 120 minutes of operation: the samples comply with the 1st fluid test, if the enteric coat of one or none of six samples is disintegrated, the enteric coating film is ruptured, peeled off, or otherwise broken, and active substance has leaked. If two of six samples are disintegrated, repeat the test with 6 additional samples. The samples comply with the test, when all six samples show no distinct evidence of disintegration.

(b) The test with the 2nd fluid

Carry out the test with new 6 samples using the 2nd fluid as the test fluid, and observe the samples after 60 minutes of operation with auxiliary disks: the samples comply with the test, if no residue, only the film of the preparation or spongy substances, or only a small amount of a soft residue or a muddy substance remains in the glass tube.

(ii) Granules and capsules enclosing drugs in granular form

Perform the following two tests, (a) the test with the 1st fluid and (b) the test with the 2nd fluid.

(a) The test with the 1st fluid

Shake granules or contents taken out from capsules on a No.30 (500 μm) sieve as directed in (1) Granules under the Particle Size Distribution Test for Preparations, transfer 0.10 g of the residue on the sieve to each of the 6 auxiliary tubes, secure the 6 tubes to the bottom of the basket tightly, and carry out the test using the 1st fluid as the test fluid. Observe the residue after 60 minutes of operation: the samples comply with the test, if particles fallen from the openings of the wire gauze number not more than 15.

(b) The test with the 2nd fluid

Transfer 0.10 g of the residue, obtained by the same way as directed in the test with the 1st fluid, to each of the 6 auxiliary tubes, secure the 6 tubes to the bottom of the basket tightly, and operate the apparatus using the 2nd fluid as the test fluid for 30 minutes, and observe the samples: the samples comply with the test, if no residue remains in any of the auxiliary tubes or only one sample remains intact, or if the residue is the film of the samples, or is only a small amount of a soft residue or a muddy substance.

# 15. Dissolution Test

The Dissolution Test is a method to test the dissolution of active ingredients from solid preparations for internal use, and aims at confirming the quality of solid preparations for internal use in relation to a fixed standard and also at preventing significant bioinequivalence.

**Apparatus**

All parts of the apparatus that may come into contact with the preparation or the dissolution medium must be chemically inert and do not adsorb or react or interfere with the test substance. Usually, all metal parts of the apparatus that may come into contact with the dissolution medium are made from a suitable stainless steel or coated with an inert material. A vessel for the sample and the dissolution medium that permits observation of the inside during the test is preferable.

(1) Method 1 (Rotatory basket method)

The testing assembly consists of a vessel with a hemispherical bottom as shown in Fig. 1, a cylindrical basket and a rotatory shaft as shown in Fig. 2, an electric motor and a thermostat. Capacity of the vessel is about 1000 mL. The lower end of the rotatory shaft is connected to a coupling disk with three clasps which are fitted on top of the basket. The side wall and the lower part of the cylindrical basket are formed by fixing a No. 36 (425 μm) sieve to two rings at the upper and the lower end. The basket is fitted in the coupling disk and the upper end of the rotatory shaft is terminated in a shaft bearing which is devised to transmit the rotatory movement of the motor.

(2) Method 2 (Paddle method)

The testing assembly consists of a round bottom vessel shown in Fig. 1, a paddle shown in Fig. 3, an electric motor and a water bath with a thermostat. The paddle conforms to the specification shown in Fig. 3. The blade is positioned horizontally at the end of the shaft so that the 42.0 mm-edge is on the same level as the lower end of the shaft and the blade passes through the center of the shaft. The upper end of the paddle shaft is terminated in a shaft bearing which is devised to transmit the rotatory movement of the motor. A sinker with 12.0 ± 0.2 mm in inside diameter and 25 – 26 mm in length shown in Fig. 4 may be used when the sample floats in the dissolution medium. The trunk of the sinker consists of a spiral 3.0 – 3.5 mm pitch coil made with an acid-resistant 1 mm thick wire. The spiral is supported on the outside with 10 wires which are fixed almost in parallel and with an equal distance. The sides of the sinker are fixed with two

double wires in a cross shape but on one of sides it is fixed with a clasp and can be opened so that a sample can be inserted.

**(3)** Method 3 (Flow-through cell method)

The apparatus consists of a cylindrical cell with a cone-shaped bottom, constant flow pump, reservoir for the dissolution medium, tubes and thermostat, as shown in Fig. 5. Generally, the dissolution medium pumped out from the reservoir is collected in collection receptacles after flowing through the cell as illustrated in Fig. 5. The test may be performed in a circulating system where the dissolution medium comes back to the reservoir after passing through the cell. In this case, the dissolution medium in the reservoir should be mixed by a suitable method to unify the concentration of the medium. There are two kinds of the cell, a large one and a small one, as shown in Fig. 6a and Fig. 6b, respectively. The cell is mounted vertically and a glass bead 5 ± 0.5 mm in diameter is placed at the bottom of the cell and then an amount of glass beads 1.0 ± 0.1 mm in diameter is put on it to make the surface flat. A filter system preventing escape of undissolved particles and diluent is fixed on the upper part of the cell with a clamp. Sample holders shown in Fig. 7a and Fig. 7b are available, and, fixed at the score mark in the cell, they keep the sample at the middle of the cell. The cell is immersed in the thermostat bath to maintain it at 37 ± 0.5°C. The pump speed must be not more than 130 pulses per minute, and the flow profile must be sinusoidal. Generally, the test is performed at a flow rate of 4, 8 or 16 mL per minute. Tubes 1.6 to 2.0 mm in inside diameter are connected to the cell, the pump and the reservoir. The shortest possible tube is preferable.

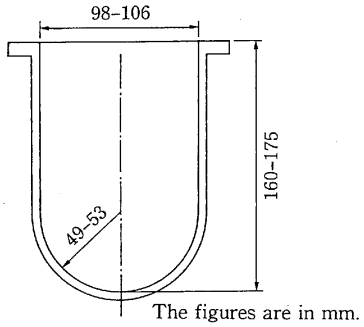
**Dissolution medium**

Generally, the dissolution medium is deaerated by a suitable method prior to use. If the dissolution medium is buffered, adjust its pH to within ±0.05 of the prescribed value.

**Procedure**

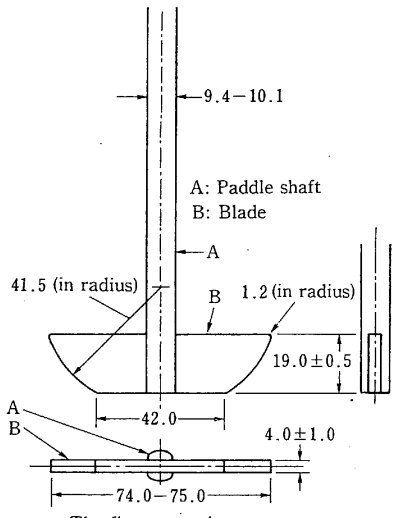
**(1)** Method 1 and Method 2

Transfer a definite volume of the dissolution medium specified in the individual monograph to a vessel, and maintain the temperature of the dissolution medium at 37 ± 0.5° C. Fit the testing assembly to the shaft bearing, and adjust the apparatus so as to rotate at ±4% of the rate specified in



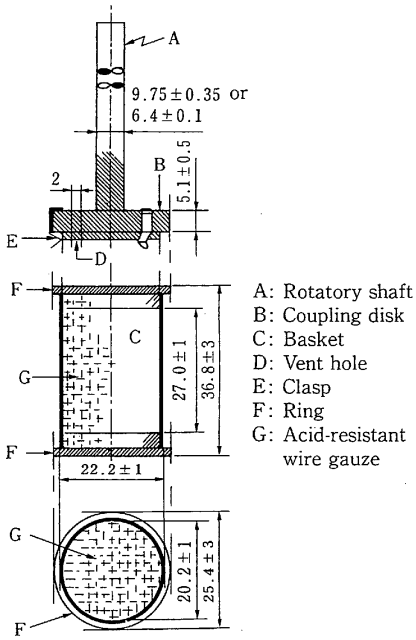

The figures are in mm.

**Fig. 1**



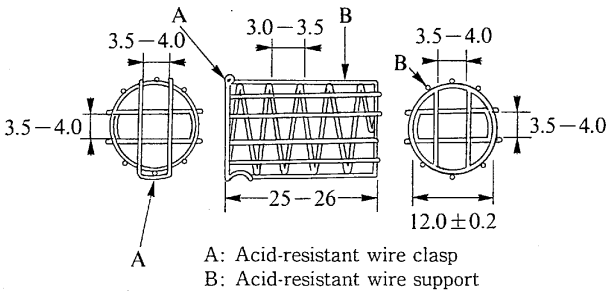

The figures are in mm.

**Fig. 3**




The figures are in mm.

**Fig. 2**




The figures are in mm.

**Fig. 4**

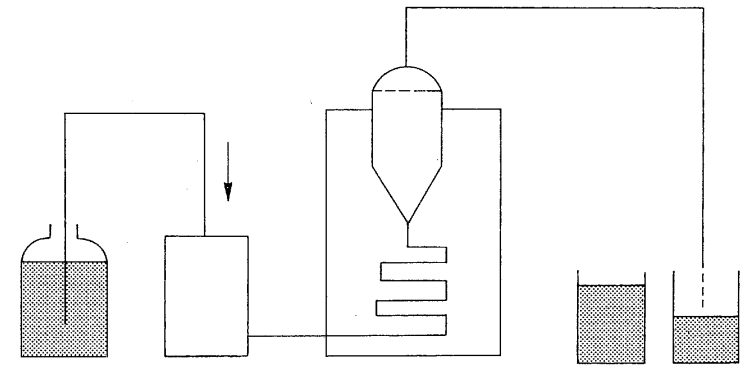
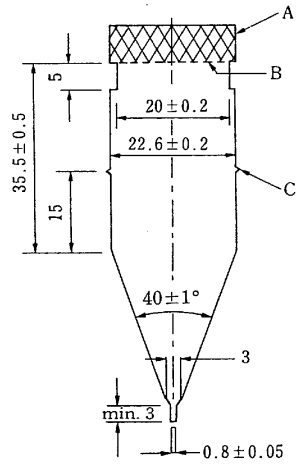


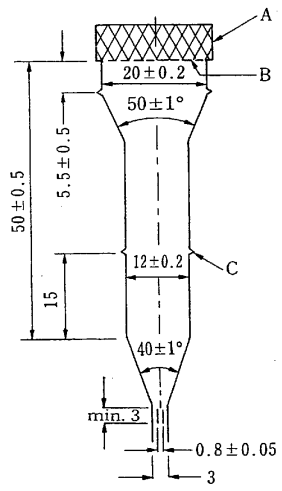

**Fig. 5**




The figures are in mm.

A: Filter chamber
B: No. 36 sieve (0.425 mm) or wire gauze (d: 0.2 mm, w: 0.45 mm)
C: Score for the sample holder

**Fig. 6a**




The figures are in mm.

**Fig. 6b**

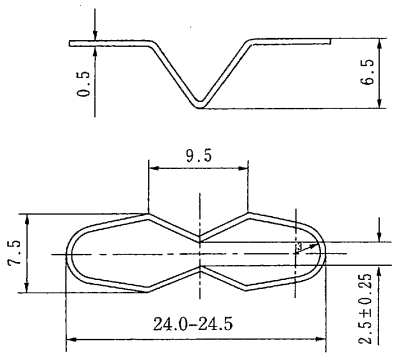



**Fig. 7a**

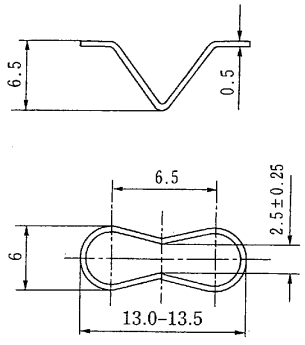



**Fig. 7b**

The figures are in mm.

the individual monograph. Fix the testing assembly to the shaft bearing so that a distance between the lower end of the basket or paddle and the inside bottom of the vessel is maintained at 25 ± 2 mm, and the axis of the rotatory shaft is not more than 2 mm from the vertical axis of the vessel. During the operation, remove the thermometer, cover the vessels in order to prevent evaporation of the dissolution medium, and ensure that the stirring element rotates smoothly without significant agitation or vibration. When Method 1 is performed, unless otherwise specified, place one sample in the dry basket, fit the basket to the coupling disk, lower the basket to a specified position, and immediately start rotation. When Method 2 is performed, unless otherwise specified, allow one sample to sink to the center of the vessel, and immediately start rotation of the paddle at a specified position. If the use of the sinker is specified in the individual monograph, place the sample in the sinker and allow to sink to the center of the vessel.

(2) Method 3

In a cell, specified in the individual monograph, place one glass bead 5 mm in diameter and a specified amount of glass beads 1 mm in diameter, and, unless otherwise specified, place one sample on the layer of glass beads, or on a holder in the case where the use of a holder is specified in the individual monograph. After assembling a specified filter, introduce the dissolution medium warmed to 37 ± 0.5°C through the bottom of the cell to obtain a suitable flow rate within ± 5% of the prescribed rate by using a pump. Use a pump with suitable pulse flow characteristics, if specified in the monograph.

**Sampling of the dissolution medium**

When only a lower limit of the dissolution rate is specified at a point of time in the individual monograph, collect the dissolution medium at a prescribed time. However, in the case where the sample meets the requirement of the dissolution test, the dissolution medium may be collected at a time before the prescribed time, and the test may be halted. When two or more points of withdrawal time or both upper and lower limits of the dissolution rate are specified in the monograph, collect the dissolution medium at the prescribed time within a tolerance of ±2%.

In Method 1 and Method 2, collect a volume of the dissolution medium from a position midway between the surface of the dissolution medium and the top of the basket or blade and not less than 10 mm from the vessel wall, filter immediately by a suitable method, and use the filtrate as the sample solution. For the filtration, an inert filter must be used that does not adsorb the active ingredient from the solution and does not contain substances extractable by the dissolution medium that would interfere with the prescribed analytical method. In Method 3, the dissolution medium that emerges from the cell and collected in the receptacles or the medium in the reservoir is used as the sample solution.

The active ingredient in the sample solution is assayed by a method described in the individual monograph, and the quantity dissolved in a specified time is expressed as a percentage of the labeled amount.

**Determination**

Unless otherwise specified, perform the test on 6 samples: if the individual dissolution rate obtained from each sample meets the requirements specified in the individual monograph, the samples conform to the test. When individual dissolution rates of 1 or 2 samples fail to meet the requirements, repeat the test on 6 additional samples: if individual dissolution rates of not less than 10 samples out of 12 meet the requirements, the samples conform to the test.

# 16. Endpoint Detection Methods in Titrimetry

Titrimetry is a method or a procedure for volumetric analysis, which is usually classified into acid-base titration (neutralization titration or pH titration), precipitation titration, complexation titration, oxidation-reduction titration, etc., according to the kind of reaction or the nature of the phenomenon occurring between the titrate and the titrant (standard solution for volumetric analysis). Furthermore, titration performed in a nonaqueous solvent is generally called nonaqueous titration, which is frequently used for volumetric analysis of weak acids, weak bases, and their salts. The endpoint in titrimetry can be detected by color changes of indicators and/or by changes of electrical signals such as electrical potential or electrical current.

The indicator method is one of the endpoint detection methods in titrimetry. In this method the color of an indicator dye, dissolved in the titrate, changes dramatically in the vicinity of the equivalence point due to its physico-chemical character, and this property is used for visual endpoint detection. Selection of an indicator and specification of the color change induced in the respective titration system, should be described in the individual monograph. An appropriate indicator should change color clearly, in response to a slight change in physico-chemical properties of the titrate, such as pH, etc., in the vicinity of the equivalence point.

Regarding the electrical endpoint detection methods, there are an electrical potential method and an electrical current method, which are called potentiometric and amperometric titration methods, respectively. They are generically named electrometric titration. In the potentiometric titration method, the endpoint of a titration is usually determined to be the point at which the differential potential change becomes maximum or minimum as a function of the quantity of titrant added. In the amperometric titration method, unless otherwise specified, a bi-amperometric titration method is used, and the endpoint is determined by following the change of microcurrent during the course of a titration. Furthermore, the quantity of electricity (electrical current × time) is often used as another electrochemical signal to follow a chemical reaction, as described in "*Water Determination 2. Coulometric Titration*".

The composition of a titration system, such as amount of specimen, solvent, standard solution for volumetric analysis, endpoint detection method, equivalent amount of substance to be examined (mg)/standard solution (mL), should be specified in the individual monograph. Standardization of the standard solution and titration of a specimen are recommended to be done at the same temperature. When there is a marked difference in the temperatures at which the former and the latter are performed, it is necessary to make an appropriate correction for the volume change of the standard solution due to the temperature difference.

**Indicator Method**

Weigh an amount of a specimen in a flask or a suitable vessel as directed in the monograph or in "*Standard Solutions*