t_R: Retention time of compound,
$W_{0.5\,h}$: Width of the peak at half peak height,

where t_R and $W_{0.5\,h}$ have the same unit.

Note: Avoid the use of authentic specimens, internal standards, reagents or solvents containing substances that may interfere with the determination.

Among the operating conditions specified in the individual monograph, inside diameter and length of the column, particle size of the column packing material, column temperature, composition ratio of the mobile phase, composition of buffer solutions in the mobile phase, pH of the mobile phase, concentration of ion pair-forming agents in the mobile phase, ionic strength of the mobile phase, numbers of condition changes, timing of such changes, gradient program, composition and flow rate of derivative-producing reagents, reaction time and temperature of reaction chamber and flow rate of mobile phase may be modified within limits which allow the required elution order, resolution, symmetry factor, and relative standard deviation to be obtained.

28. Loss on Drying Test

The Loss on Drying Test is a method to measure the loss in mass of the sample, when dried under the conditions specified in each monograph. This method is applied to determine the amount of water, all or a part of water of crystallization, or volatile matter in the sample, which is removed during the drying.

The description, for example, "not more than 1.0% (1 g, 105°C, 4 hours)" in a monograph, indicates that the loss in mass is not more than 10 mg per 1 g of the substance in the test in which about 1 g of the substance is accurately weighed and dried at 105°C for 4 hours, and "not more than 0.5% (1 g, in vacuum, phosphorus (V) oxide, 4 hours)," indicates that the loss in mass is not more than 5 mg per 1 g of the substance in the test in which about 1 g of the substance is accurately weighed, transferred into a desiccator (phosphorus (V) oxide), and dried in vacuum for 4 hours.

Procedure

Weigh assurately a weighing bottle that has been dried for 30 minutes according to the method specified in the monograph. Take the sample within the range of ±10% of the amount directed in the monograph, transfer into the weighing bottle, and, unless otherwise specified, spread the sample so that the layer is not thicker than 5 mm, then weigh it accurately. Place the loaded bottle in a drying chamber, and dry under the conditions specified in the monograph. When the size of the sample is large, convert it to small particles having a size not larger than 2 mm in diameter by quick crushing, and use the crushed sample for the test. After drying, remove from the drying chamber, and reweigh accurately. When the sample is dried by heating, the temperature is within the range of ±2°C of that directed in the monograph, and, after drying the bottle, the sample is allowed to cool in a desiccator (silica gel) before weighing.

If the sample melts at a temperature lower than that specified in the monograph, expose the sample for 1 to 2 hours to a temperature between 5°C and 10°C below the melting temperature, dry under the conditions specified in the monograph. Use a desiccant specified in the monograph, and renew frequently.

29. Loss on Ignition Test

The Loss on Ignition Test is a method to measure the loss in mass when the sample is ignited under the conditions specified in each monograph. This method is usually applied to inorganic drugs which lose a part of the components or impurities during ignition.

The description, for example, "40.0 – 52.0% (1 g, 450 – 550°C, 3 hours)" in a monograph, indicates that the loss in mass is 400 to 520 mg per g of the substance in the test in which about 1 g of the substance is weighed accurately and ignited between 450°C and 550°C for 3 hours.

Procedure

Previously ignite a crucible or a dish of platinum, quartz or porcelain to constant mass, at the temperature directed in the monograph, and weigh accurately after cooling.

Take the sample within the range of ±10% of the amount directed in the monograph, transfer into the above ignited container, and weigh it accurately. Ignite under the conditions directed in the monograph, and, after cooling, reweigh accurately. Use a desiccator (silica gel) for the cooling.

30. Mass Variation Test

Mass Variation Test is the test to determine the uniformity of dosage units by mass variation. This test is not applied to the dosage forms to which *Content Uniformity Test* is applied. Apply the following test unless otherwise specified in the individual monograph. The *Content Uniformity Test* can be employed for this test when the method directed in the *Assay* is used for determination.

Select 30 units, weigh the first 10 units individually and calculate the acceptance value. The requirements are met if the acceptance value is less than or equal to 15.0%. When the acceptance value is greater than 15.0%, test the next 20 units. The requirements are met if the final acceptance value of the 30 dosage units does not exceed 15.0% and no unit shows a deviation that exceeds 25.0% of the label claim.

$$\text{Acceptance value} = |M - A| + ks$$

M: Label claim (100%), unless otherwise specified in the individual monograph.
A: Content of active ingredient (% of label claim) determined under Assay.

$$x_i = w_i \times A/\overline{W}$$

$x_1, x_2 \cdots x_i \cdots x_n$: Individual estimated contents of the units tested.
$w_1, w_2 \cdots w_i \cdots w_n$: Individual masses of the units tested.
$\overline{W}$: Mean of individual masses ($w_1, w_2 \cdots w_i \cdots w_n$).
n: Sample size (number of units in a sample).
k: Acceptability constant, $k = 2.2$ when the sample size is 10, and $k = 1.9$ when the sample size is 30.
s: Standard deviation of the sample.

$$s = \sqrt{\frac{\sum_{i=1}^{n} (x_i - A)^2}{n - 1}}$$

Proceed by the following method for the dosage form designated.

Capsules and Solids (Granule, Powder, Syrup) in single-unit container

Assume the individual masses of intact units as the mass of the preparation and apply the above test. If the requirement was not met, measure the net mass by the following methods and apply the above test.

1. Hard Capsules and Solids (Granule, Powder, Syrup) in single-unit container

Weigh accurately individual units, taking care to preserve the identity of each unit. Remove the contents of each unit by a suitable means such as brushing. Weigh accurately the emptied shells individually, and calculate for each unit the net mass of its contents by subtracting the mass of the shell from the respective gross mass.

2. Soft Capsules

Weigh accurately individual units, taking care to preserve the identity of each unit. Cut open the capsules and remove the contents by washing with a suitable volatile solvent (e.g., diethyl ether). Allow the occluded solvent to evaporate from the shells at room temperature, taking precautions to avoid uptake or loss of moisture. Weigh accurately the emptied shells individually, and calculate for each unit the net mass of its contents by subtracting the mass of the shell from the respective gross mass.

Injections (to be dissolved or suspended before use)

Wash the containers of individual units after removal of paper labels, if these exist, and dry them completely. Open carefully the containers and weigh accurately all parts of the opened containers, taking care to preserve the identity of each unit. Remove the contents of each unit by washing sufficiently with water and ethanol (95), and dry them completely. Weigh accurately all parts of the cleaned containers individually, and calculate for each unit the net mass of its contents by subtracting the mass of the container from the respective gross mass.

31. Melting Point Determination

The Melting Point refers to the temperature determined by the following methods. When the melting point of a substance is given as a range, the substance should melt within that range of temperature.

Three procedures are provided for the determination depending upon the nature of the substance. Unless otherwise specified, proceed by Method 1.

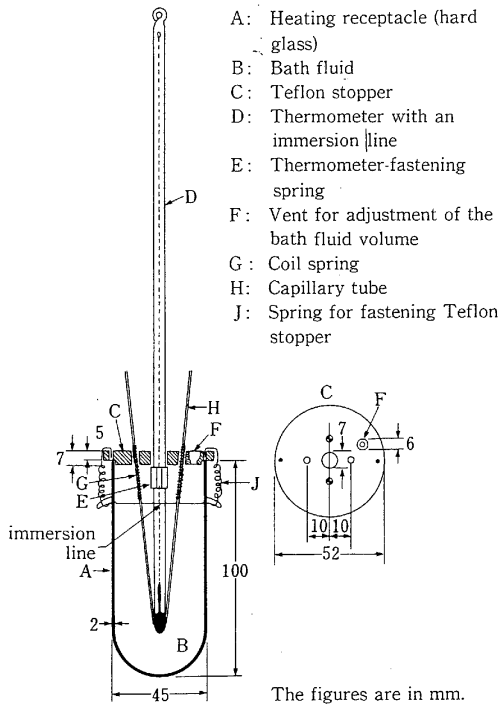
Method 1 This method is applied to those substances that can be readily reduced to fine powders.

(1) Apparatus

Use the apparatus illustrated in the figure.

Bath fluid: Use clear silicone oil having the viscosity of 50 to 100 mm^2/s at ordinary temperature.

Thermometer with an immersion line: For meltimg points



The figures are in mm.

lower than 50°C, use a thermometer Type 1; for 50°C to 100°C, Type 2; for 100°C to 150°C, Type 3; for 150°C to 200°C, Type 4; for 200°Cto 250°C, Type 5; for 250°C to 320°C, Type 6.

Capillary tube: Use a hard glass capillary tube 120 mm long, 0.8 to 1.2 mm in inner diameter and with walls 0.2 to 0.3 mm thick; one end is closed.

(2) Procedure

Reduce the sample to a fine powder, and, unless otherwise specified, dry in a desiccator (silica gel) for 24 hours. When it is specified to do the test after drying, dry the sample under the conditions in the test for Loss on Drying before the detemination. Place the sample in a dried capillary tube H, and pack the sample tightly in a layer about 3 mm in height by dropping it repeatedly, with the closed end of H down, through a glass tube, about 70 cm long, held vertically on a glass or porous plate.

Heat the bath fluid B until the temperature rises to about 10°C below the expected melting point, place the immersion line of the thermometer D at the same level as the meniscus of the bath fluid, and insert capillary tube H into coil spring G so that the sample is on a level with the middle of the mercury bulb of the thermometer D. Then continue the heating to raise the temperature at a rate of approximately 3°C per minute until the temperature rises to 5°C below the expected melting point, then carefully regulate the rate of increase to 1°C per minute.

Read the indication of the thermometer D at the point at which the sample liquefies throughout and no solid is visible in the capillary tube H, and designate the temperature as the melting point.

Method 2 This method is applied to such substances as fats, fatty acids, paraffins or waxes, that are insoluble in water and not readily reduced to powder.

Procedure

Carefully melt the sample at as low a temperature as possi-