

place 5 mL of sulfuric acid for readily carbonizable substances in a Nessler tube, to which add a quantity of the finely powdered sample, little by little, as directed in the monograph, and dissolve it completely by stirring with a glass rod. When the sample is liquid, transfer a volume of the sample, as directed in the monograph, to a Nessler tube, add 5 mL of sulfuric acid for readily carbonizable substances, and mix by shaking. If the temperature of the content of the tube rises, cool the content; maintain it at the standard temperature, if the reaction may be affected by the temperature. Allow to stand for 15 minutes, and compare the color of the liquid with that of the matching fluid in the Nessler tube specified in the monograph, by viewing transversely against a white background.

50. Refractive Index Determination

The Refractive Index Determination is a method to measure the ratio of the velocity of light in air to that in the sample. Generally, when light proceeds from one medium into another, the direction is changed at the boundary surface. This phenomenon is called refraction. When light passes from the first isotropic medium into the second, the ratio of the sine of the angle of incidence, i , to that of the angle of refraction, r , is constant with regard to these two media and has no relation to the angle of incidence. This ratio is called the refractive index of the second medium with respect to the first, or the relative refractive index, n .

$$n = \frac{\sin i}{\sin r}$$

The refractive index obtained when the first medium is a vacuum is called the absolute refractive index, N , of the second medium.

In isotropic substances, the refractive index is a characteristic constant at a definite wavelength, temperature, and pressure. Therefore, this measurement is applied to purity test of substances, or to determination of the composition of homogeneous mixtures of two substances.

The measurement is usually carried out at 20°C, and the D line of the sodium spectrum is used for irradiation. This value is expressed as n_D^{20} .

Procedure

For the measurement of refractive index, usually the Abbé refractometer is used at a temperature in the range of $\pm 0.2^\circ\text{C}$ of that directed in the monograph. Use of the Abbé refractometer permits direct reading of n_D under incandescent light, with a measurable range from 1.3 to 1.7, and an attainable precision of 0.0002.

51. Residual Solvents Test

The Residual Solvents Test is a test to determine the amounts of residual organic solvents in pharmaceuticals by using the Gas Chromatography to monitor adherence to the limits which are advised for the safety of patients by "Guideline for Residual Solvents: ICH Harmonized Tripartite

Guideline".

Unless otherwise specified, the limit of the residual solvents is described in ppm in the individual monograph, and unless otherwise specified, the limit should be not more than the limit advised in the Guideline.

Apparatus, Procedure, and Test Method

Prepare the sample solution and the standard solution as directed in the relevant monograph, and perform the test as directed under the Gas Chromatography.

In monographs, the quantity for the test of sample and reference standard (reference substances), the method for preparation of the sample and standard solutions, the injection amount of the sample and standard solutions for the gas chromatography, the operating conditions for the headspace apparatus and the gas chromatography, the system suitability, the calculation formula, and other items concerning the test are specified.

52. Residue on Ignition Test

The Residue on Ignition Test is a method to measure the mass of the residual substance not volatilized when the sample is ignited by the method described below. Generally, this test is intended for determining the content of inorganic substances contained as impurities in an organic substance, and, occasionally, for determining the amount of inorganic substances contained as components in an organic substance, or the amount of impurities contained in a volatile inorganic substance.

The description, for example, "not more than 0.10% (1 g)," in a monograph, indicates that the mass of the residue is not more than 1.0 mg per 1 g of the substance in the test in which about 1 g of the substance is weighed accurately and ignited by the procedure described below, and "after drying" indicates that the sample is tested after being dried under the conditions specified in the test for Loss on drying.

Procedure

Previously ignite a crucible of platinum, quartz or porcelain to constant mass between 450°C and 550°C, and weigh accurately after cooling.

Take the sample within the range of $\pm 10\%$ of the amount directed in the monograph, transfer into the above ignited container, and weigh it accurately. When the quantity of the sample to be taken is indicated in a volume, pipet exactly the amount directed in the monograph and transfer into the above ignited container. When directed as "after evaporating," heat properly to evaporate the solution.

Moisten the sample with a few drops of sulfuric acid, then heat slowly at a temperature as low as practicable until the sample is almost incinerated or volatilized, and cool it. Moisten again with a small amount of sulfuric acid, heat gently until white fumes are evolved no longer, and ignite between 450°C and 550°C until the residue is completely incinerated. Cool the crucible and reweigh accurately. Use a desiccator (silica gel) for the cooling.

When the specification of the residue on ignition in the monograph is described as "not more than % or mg," and the amount of the residue obtained above exceeds the limit specified in the monograph, or when the specification is described with a certain range, ignite repeatedly to constant

mass.

53. Specific Surface Area Determination

The gas adsorption method is a method for measuring the amount of gas adsorbed on the surface of a powder sample as a function of the pressure of the adsorbate gas, and is used to determine the specific surface area of a powder sample. Measurements are usually performed at the boiling point of liquid nitrogen (-196°C).

When the gas is physically adsorbed by the powder sample, the following relationship holds when P/P_0 is in the range of 0.05 to 0.30 for pressure P of the adsorbate gas in equilibrium for the volume of gas adsorbed, V_a .

$$\frac{1}{V_a \left(\frac{P_0}{P} - 1 \right)} = \frac{(C - 1)}{V_m C} \times \frac{P}{P_0} + \frac{1}{V_m C}$$

P : Partial vapor pressure of adsorbate gas in equilibrium (kPa)

P_0 : Saturated pressure of the adsorbate gas at -196°C (kPa)

V_a : Volume of gas adsorbed at equilibrium (mL)

V_m : Volume of gas adsorbed in a monolayer (mL)

C : Dimensionless constant related to the enthalpy of adsorption and condensation of the adsorbate gas

The specific surface area, S , is determined from V_m , the volume of gas adsorbed in a monolayer on the sample.

$$S = \frac{V_m \times N \times a}{m \times 22400}$$

S : Specific surface area (m^2/g)

N : Avogadro constant

a : Effective cross-sectional area of one adsorbate molecule (m^2)

m : Mass of the test powder (g)

Specific surface area is generally expressed in units of m^2/g .

Either of the methods described below can be used to measure the gas adsorption.

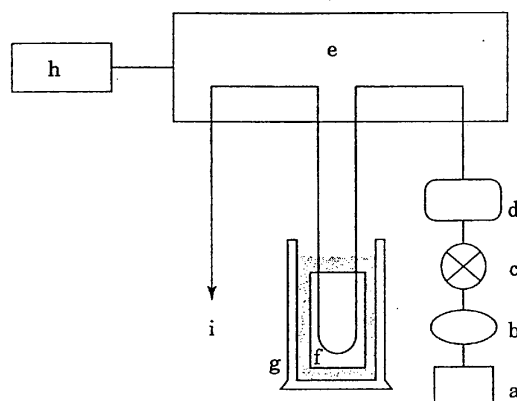
Method 1 Dynamic Flow Method

In the dynamic flow method, a mixture of the adsorbate gas and a carrier gas is passed over a sample, and the volume of gas adsorbed is determined from the change in the concentration of the adsorbate gas in the mixture before and after the exposure to the powder sample. Nitrogen is typically used as the adsorbate gas, and a gas such as krypton is preferred for samples with a small specific surface area. Helium is generally used as the diluent gas.

Equipment

The test equipment typically comprises a sample container, a gas supply unit, a gas mixing unit, a gas flow regulator, a gas concentration detector, and a Dewar vessel. The sample container is made from glass and is formed in an U-shape to allow smooth gas flow. The gas flow path can be sealed to form an airtight passage. There are two gas supply units; one for the adsorbate gas, and one for the diluent gas.

The adsorbate and diluent gases are mixed in the mixing unit, and the concentration of the adsorbate gas in the mixture can be varied within the range of 5 to 30 vol%. The gas flow regulator equipped with a gas flow meter is used to adjust the flow volume of the gas mixture supplied to the sample container. A thermal conductivity detector is generally used as a gas concentration detector to observe variations in the concentrations of the adsorbate gas in the gas mixture. The Dewar vessel holds the liquid nitrogen used to cool the sample container.



- | | |
|------------------------------|---|
| a Gas supply unit | f Sample container |
| b Gas mixing unit | g Dewar vessel |
| c Gas flow regulator | h Recording equipment, data processor, and recorder |
| d Cooling unit | i Gas outlet |
| e Gas concentration detector | |

Procedure

Precisely weigh the sample container. Place a quantity of the test powder having a total surface area of at least 1 m^2 in the sample container. Perform pretreatment to remove any gases and vapors that have been physically adsorbed onto the sample surface. The pretreatment is performed by exposing the test powder to a continuous flow of a nonreactive gas or the gas mixture to be used for the measurements. Heating may also be employed as long as there is no effect on the physical or chemical properties of the sample. Outgassing may also be achieved by placing the sample container in a vacuum. After the pretreatment is completed, precisely weigh the sample container with the sample and subtract the mass of the tared container measured previously, to obtain the mass of the test powder.

During the outgassing operate the gas mixing unit and the flow regulator so that a gas mixture containing a fixed ratio of the gases flows through the system. Pass a known volume of about 1 mL of the pure adsorbate gas and record the output from the gas concentration detector, and integrate the area under the peak. Then connect the sample container to the gas concentration detector and pass the gas mixture through the system again. Set the Dewar vessel so that the sample container is immersed in the liquid nitrogen, record the output signal caused by gas adsorption and integrate the area under the peak. By comparing the two integral values, the adsorbed volume of gas can be calculated. Next, lower the Dewar vessel from the sample container and quickly bring the sample container to room temperature. The peak obtained under this condition shows the desorption signal of