

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.

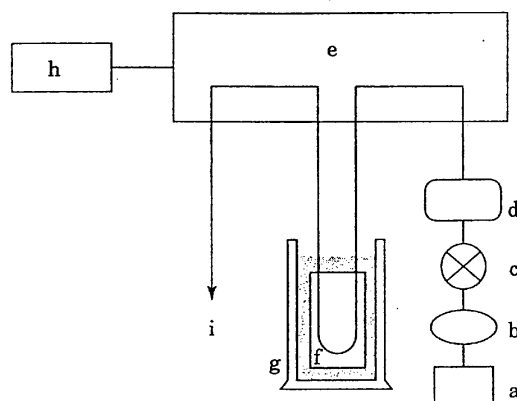
Method 1 Dynamic Flow Method

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.



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

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

the adsorbate gas. Determine the integral value and calculate the desorbed volume by using this value.

Repeat the measurements with at least three different gas mixtures, varying the ratio of the gases in the mixture by operating the gas mixing unit. For the dynamic flow method, the mix ratio of gases is the relative pressure for the surface area calculation. The volume of gas desorbed is typically used as the volume of gas adsorbed.

Method 2 Volumetric Method

In the volumetric method, the test powder is placed in a sample container with a known volume and the volume of gas adsorbed is determined from the change in pressure associated with the adsorption of gas on the surface of sample powder. Nitrogen is typically used as the adsorbate gas, and a gas such as krypton is preferred for samples with a small specific surface area.

Equipment

The test equipment typically comprises a sample container, a gas supply unit, a calibrated volume section, a vacuum pump, a pressure gauge, a vacuum meter, and a Dewar vessel. The sample container is made from glass, and can be easily attached and detached from the main unit so that pretreatment of the sample can be performed easily. The Dewar vessel is used to hold the liquid nitrogen used to cool the sample container. The void volume indicates the total volume of space in the system that is occupied by the adsorbate gas, including the sample container after the powder sample is placed, in it, the pressure gauge, and the connected system. The void volume should be kept as small as possible to allow measurement of the volume of the gas adsorbed with higher accuracy.

Procedure

Precisely weigh the tared sample container. Place a quantity of the test powder having a total surface area of at least 1 m² in the sample container. Perform pretreatment to remove any gases and vapors that have been physically adsorbed onto the sample surface, by outgassing the sample under reduced pressure. Heating may also be employed as long as there is no effect on the physical or chemical properties of the sample. 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.

Take a fixed quantity of the adsorbate gas and introduce it into the sample container that has been chilled by immersion in liquid nitrogen. The adsorbate gas is adsorbed on the powder sample. The pressure decreases until gas/solid adsorption reaches to a new equilibrium. The volume of gas adsorbed is calculated from the difference between the volume of adsorbate gas that was introduced and the volume of unadsorbed gas remaining in the void volume. The void volume is measured by using helium either before or after the adsorption measurements are performed.

For the multiple-point BET method, calculate the specific surface area by repeating 3 measurements or more of the volume adsorbed, under a relative equilibrium pressure of the adsorbate gas in the range from 0.05 to 0.30. For the single-point method, make one measurement of the volume adsorbed, under a relative pressure of close to 0.30.

Equipment Calibration

The equipment calibration is performed by using α -alumi-

na for specific surface area determination. Measure the specific surface area of the α -alumina according to the specified method. The specific surface area obtained must be within the range specified for the reference standard of α -alumina. The α -alumina for specific surface area determination must be pre-processed according to the specified method.

54. Sterility Test

The test is a method to establish the presence or absence of viable microorganisms (bacteria and fungi) using the defined culturing method. Unless otherwise indicated, the test is carried out by I. Membrane filtration method or II. Direct transfer method. The test should be conducted by personnel well trained in aseptic techniques and the results should be interpreted by personnel having basic knowledge of general microbiology.

Water, reagents, test solutions, equipment, materials and all other requisites for the test should be presterilized. All the operations should be conducted with proper precautions to maintain sterility in an aseptic facility or in aseptic equipment controlled under Grade A conditions as described in the chapter entitled "Microbiological Evaluation of Processing Areas for Sterile Pharmaceutical Products".

Media, rinsing fluids and their preparation

Thioglycollate medium I for sterility test and soybean-casein digest medium are used, unless otherwise specified. When it is difficult to use thioglycollate medium I for sterility test due to turbidity or viscosity of samples, thioglycollate medium II for sterility test can be used, provided it is heated on a water bath just prior to use and incubated under anaerobic conditions. Other products of suitable quality yielding similar formulations may be used according to the indications on the label.

(I) Thioglycollate medium I for sterility test

L-Cystine	0.5 g
Agar	0.75 g
Sodium chloride	2.5 g
Glucose	5.0 g
Yeast extract	5.0 g
Casein peptone	15.0 g
Sodium thioglycollate	0.5 g
Resazurin solution (1 in 1000)	1.0 mL
Water	1000 mL

(pH after sterilization: 6.9 – 7.3)

Mix all the ingredients and heat until solution is effected. If necessary, adjust the pH of the solution with sodium hydroxide TS so that, after sterilization, it will show 6.9 to 7.3. Filter while hot through moistened filter paper, if necessary. Mix thoroughly, place the required volume of the medium in suitable containers, which provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a color change at the end of the incubation period, and sterilize in an autoclave using a validated process. Store the medium at room temperature, protected from light. Do not use the medium when its fluidity shows any change owing to evaporation of water during storage or when the upper one-third or more has acquired a pink color.