

iodine-starch TS is added dropwise to the filtrate, the color of the test solution disappears.

(4) Acidic solutions of stannic salts in hydrochloric acid, to which ammonia TS is added dropwise until a small quantity of precipitate is produced, yield a pale yellow precipitate with 2 to 3 drops of sodium sulfide TS. The separated precipitate dissolves upon addition of sodium sulfide TS and pale yellow precipitate is reproduced by subsequent addition of hydrochloric acid.

#### **Stannous salt**

(1) When the outside bottom of a test tube containing water is moistened with acidic solutions of stannous salts in hydrochloric acid and is placed in a nonluminous flame of a Bunsen burner, a blue flame mantle is seen around the bottom of the test tube (common with stannic salts).

(2) When granular zinc is immersed in acidic solutions of stannous salts in hydrochloric acid, a spongy, gray substance is deposited on the surface of the granules (common with stannic salts).

(3) When iodine-starch TS is added dropwise to solutions of stannous salts, the color of the test solution disappears.

(4) Acidic solutions of stannous salts in hydrochloric acid, to which ammonia TS is added dropwise until a small quantity of precipitate is produced, yield a dark brown precipitate with 2 to 3 drops of sodium sulfide TS. When sodium sulfide TS is added to a portion of the separated precipitate, it does not dissolve. When ammonium polysulfide TS is added to another portion, the precipitate dissolves.

#### **Sulfate**

(1) Solutions of sulfates yield with barium chloride TS a white precipitate, which does not dissolve upon addition of dilute nitric acid.

(2) Neutral solutions of sulfates yield with lead (II) acetate TS a white precipitate, which dissolves upon subsequent addition of ammonium acetate TS.

(3) When an equal volume of dilute hydrochloric acid is added, solutions of sulfates yield no white turbidity (discrimination from thiosulfates), and do not evolve the odor of sulfur dioxide (discrimination from sulfites).

#### **Sulfide**

Most kinds of sulfides evolve the odor of hydrogen sulfide with dilute hydrochloric acid. This gas blackens lead (II) acetate paper moistened with water.

#### **Sulfite and Bisulfite**

(1) When iodine TS is added dropwise to acidic solutions of sulfites or bisulfites in acetic acid (31), the color of the reagent fades.

(2) When an equal volume of dilute hydrochloric acid is added, solutions of sulfites or bisulfites evolve the odor of sulfur dioxide but yield no turbidity (discrimination from thiosulfates). The solutions yield immediately with 1 drop of sodium sulfide TS a white turbidity, which changes gradually to a pale yellow precipitate.

#### **Tartrate**

(1) Neutral tartrate solutions yield a white precipitate with silver nitrate TS. When nitric acid is added to a portion of the separated precipitate, it dissolves. When ammonia TS is added to another portion and warmed, the precipitate dis-

solves and metallic silver is deposited gradually on the inside wall of the test tube, forming a mirror.

(2) Solutions of tartrates exhibit a red-purple to purple color, when 2 drops of acetic acid (31), 1 drop of iron (II) sulfate TS, 2 to 3 drops of hydrogen peroxide TS and an excess of sodium hydroxide TS are added.

(3) When a solution, prepared by mixing 2 to 3 drops of a solution of resorcinol (1 in 50) and 2 to 3 drops of a solution of potassium bromide (1 in 10) with 5 mL of sulfuric acid, is added to 2 to 3 drops of solutions of tartrates, and then heated for 5 to 10 minutes on a water bath, a deep blue color is produced. The solution exhibits a red to red-orange color when poured to 3 mL of water after cooling.

#### **Thiocyanate**

(1) Solutions of thiocyanates yield a white precipitate with an excess of silver nitrate TS. When dilute nitric acid is added to a portion of the suspension, the precipitate does not dissolve. When ammonia solution (28) is added to another portion, the precipitate dissolves.

(2) Solutions of thiocyanates produce with iron (III) chloride TS a red color, which is not decolorized by addition of hydrochloric acid.

#### **Thiosulfate**

(1) When iodine TS is added dropwise to acidic solutions of thiosulfates in acetic acid (31), the color of the reagent fades.

(2) When an equal volume of dilute hydrochloric acid is added, solutions of thiosulfates evolve the odor of sulfur dioxide, and yield gradually a white turbidity, which changes to yellow on standing.

(3) Solutions of thiosulfates yield with an excess of silver nitrate TS a white precipitate, which changes to black on standing.

#### **Zinc salt**

(1) Neutral to alkaline solutions of zinc salts yield a whitish precipitate with ammonium sulfide TS or sodium sulfide TS. The separated precipitate does not dissolve in dilute acetic acid but dissolves upon subsequent addition of dilute hydrochloric acid.

(2) Solutions of zinc salts yield a white precipitate with potassium hexacyanoferrate (II) TS. When dilute hydrochloric acid is added to a portion of the suspension, the precipitate does not dissolve. When sodium hydroxide TS is added to another portion, the precipitate dissolves.

(3) Neutral to weakly acidic solutions of zinc salts yield a white precipitate, when 1 or 2 drops of pyridine and 1 mL of potassium thiocyanate TS are added.

## **49. Readily Carbonizable Substances Test**

The Readily Carbonizable Substances Test is a method to examine the minute impurities contained in drugs, which are readily colored by addition of sulfuric acid.

#### **Procedure**

Before use, wash the Nessler tubes thoroughly with sulfuric acid for readily carbonizable substances. Unless otherwise specified, proceed as follows. When the sample is solid,

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