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THE JAPANESE PHARMACOPOEIA

THIRTEENTH EDITION

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THE JAPANESE PHARMACOPOEIA

THIRTEENTH EDITION

Under the supervision of the Research and Development Division,
Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

Official from April 1, 1996

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THE SOCIETY OF JAPANESE PHARMACOPOEIA

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The Ministry of Health and Welfare Notification No. 73

In accordance with the provision of Article 41 of the Pharmaceutical Affairs Law (Law No. 145, 1960), we establish the Japanese Pharmacopoeia (hereinafter referred to as the "new Pharmacopoeia") as follows*, and will apply it from April 1, 1996. The Japanese Pharmacopoeia prescribed by the Ministry of Health and Welfare Notification No. 51 dated March 1991 according to the Law (hereinafter referred to as the "previous Pharmacopoeia") shall be abrogated on March 31, 1996. In this case, the drugs included in the previous Pharmacopoeia which have been approved before or on April 1, 1996, in accordance with the provision of Article 14 of the Law (inclusive of application *mutatis mutandis* in Article 23; the same hereinafter) [inclusive of drugs (hereinafter referred to as "drugs not requiring approval") designated as those not requiring approval to manufacture or import on March 31, 1996, in accordance with the Ministry of Health and Welfare Notification No. 104 issued in March 1994 (matters related to designation of drugs not requiring approval to manufacture or import in accordance with Paragraph 1 of Article 14 of the Pharmaceutical Affairs Law)], even though not admitted to the new Pharmacopoeia, shall be recognized to be included in the new Pharmacopoeia up to September 30, 1997, and the standards for the previous Pharmacopoeia [limited to those for such drugs] shall be recognized to conform to those for the new Pharmacopoeia. The titles and/or standards for drugs in the previous Pharmacopoeia, even though changed in the new Pharmacopoeia, shall be recognized as those in the new Pharmacopoeia up to September 30, 1997. The drugs admitted to the new Pharmacopoeia (except for those included in the previous Pharmacopoeia) which have been approved before or on April 1, 1996, (inclusive of those not requiring approval) in accordance with the provision of Article 14 of the Law shall be recognized not to be included in the new Pharmacopoeia up to September 30, 1997.

Naoto Kan
Minister of Health and Welfare

March 13, 1996

*The word "follows" here indicates the contents of Part I and Part II in the Japanese Pharmacopoeia, Thirteenth Edition (pp. 1—1064).

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(2) To 0.1 g of Low Substituted Hydroxypropylcellulose add 10 mL of water, stir and produce a turbid solution. Add 1 g of sodium hydroxide, shake until it becomes homogeneous, and use this solution as the sample solution. To 0.1 mL of the sample solution add 9 mL of diluted sulfuric acid (9 in 10), shake well, heat in a water bath for exactly 3 minutes, immediately cool in an ice bath, add carefully 0.6 mL of ninhydrin TS, shake well, and allow to stand at 25°C: a red color develops at first, and it changes to purple within 100 minutes.

(3) To 5 mL of the sample solution obtained in (2) add 10 mL of a mixture of acetone and methanol (4:1), and shake: a white, flocculent precipitate is produced.

pH To 1.0 g of Low Substituted Hydroxypropylcellulose add 100 mL of freshly boiled and cooled water, and shake: the pH of the solution is between 5.0 and 7.5.

Purity (1) Chloride—To 0.5 g of Low Substituted Hydroxypropylcellulose add 30 mL of hot water, stir well, heat on a water bath for 10 minutes, and filter the supernatant liquid by decantation while being hot. Wash the residue thoroughly with 50 mL of hot water, combine the washings with the filtrate, and add water to make 100 mL after cooling. To 5 mL of the sample solution add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.335%).

(2) Heavy metals—Proceed with 2.0 g of Low Substituted Hydroxypropylcellulose according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Arsenic Prepare the test solution with 1.0 g of Low Substituted Hydroxypropylcellulose, according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

Loss on drying Not more than 6.0% (1 g, 105°C, 1 hour).

Residue on ignition Not more than 1.0% (1 g).

Assay (i) Apparatus—Reaction flask: A 5-mL screw-cap pressure-tight glass bottle, having an inverted conical bottom inside, 20 mm in outside diameter, 50 mm in height up to the neck, 2 mL in capacity up to a height of about 30 mm, equipped with a pressure-tight septum of heat-resisting resin and also with an inside stopper or sealer of fluoroplastic.

Heater: A square-shaped aluminum block 60 to 80 mm thick, having holes 20.6 mm in diameter and 32 mm in depth, capable of maintaining the inside temperature within ± 1°C.

(ii) Procedure—Weigh accurately about 0.065 g of Low Substituted Hydroxypropylcellulose, previously dried, transfer to the reaction flask, add 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid, stopper the flask tightly, and weigh accurately. Shake the flask for 30 seconds, heat at 150°C on the heater for 30 minutes with repeated shaking at 5-minute intervals, and continue heating for an additional 30 minutes. Allow the flask to cool, and again weigh accurately. If the weight loss is less than 10 mg, use the upper layer of the mixture as the sample solution. Separately, take 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in another reaction flask, stopper tightly, and weigh accurately. Add 15 μL of isopropyl iodide for assay, and again weigh accurately. Shake the reaction flask for 30 seconds, and use the upper layer of the content as the standard solution. Perform the test as directed under the Gas Chromatography with 2 μL each of the sample solution and the standard solution according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of isopropyl iodide to that of the internal standard.

$$\text{Amount (\%) of hydroxypropoxyl group } (C_3H_7O_2) = \frac{Q_T}{Q_S} \times \frac{W_S}{\text{amount (mg) of the sample}} \times 44.17$$

W_S: Amount (mg) of isopropyl iodide in the standard solution.

Internal standard solution—A solution of *n*-octane in *o*-xylene (1 in 50).

Operating conditions—

Detector: A thermal conductivity detector or hydrogen flame-ionization detector.

Column: A glass column about 3 mm in inside diameter and about 3 m in length, packed with siliceous earth for gas chromatography, 180 to 250 μm in particle diameter, coated with methyl silicone polymer for gas chromatography at the ratio of 20%.

Column temperature: A constant temperature of about 100°C.

Carrier gas: Helium (for thermal-conductivity detector); helium or nitrogen (for hydrogen flame-ionization detector).

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 10 minutes.

Selection of column: Proceed with 2 μL of the standard solution according to the above operating conditions. Use a column giving well-resolved peaks of isopropyl iodide and the internal standard in this order.

Containers and storage Containers—Tight containers.

Hydroxypropylmethylcellulose 2208

Hydroxypropylmethylcellulose 2208 is a methyl and hydroxypropyl mixed ether of cellulose.

When dried, it contains not less than 19.0% and not more than 24.0% of methoxyl group (–OCH_3: 31.03), and not less than 4.0% and not more than 12.0% of hydroxypropoxyl group (–OC_3H_6OH: 75.09).

The kinematic viscosity of Hydroxypropylmethylcellulose 2208 is shown in square millimeter second (mm^2/s) on the label.

Description Hydroxypropylmethylcellulose 2208 occurs as white to yellowish white, powder or granules. It is odorless or has a slight, characteristic odor. It is tasteless.

It is practically insoluble in hot water, in dehydrated ethanol, in acetone and in ether.

It swells with water and becomes a clear or slightly turbid, viscous solution.

Identification (1) To 1 g of Hydroxypropylmethylcellulose 2208 add 100 mL of hot water, cool to room temperature with stirring, and use this as the sample solution. Add

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