Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets

クロルプロマジン塩酸塩･フェノバルビタール・プロメタジン塩酸塩錠

Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets contain not less than 95.0% and not more than 105.0% of the labeled amounts of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S.HCl$: 355.33), phenobarbital ($C_{12}H_{12}N_2O_3$: 232.24) and promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$: 320.88).

Method of preparation Prepare as directed under Tablets, with Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride.

Identification **(1)** To an amount of powdered Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, equivalent to 12.5 mg of Chlorpromazine Hydrochloride, add 10 mL of ethanol (95), shake, filter, and use the filtrate as the sample solution. Separately, dissolve 12.5 mg of chlorpromazine hydrochloride for assay in 10 mL of ethanol (95), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethylamine (50:1) to a distance of about 10 cm, and air-dry the plate. Again, develop the plate with the same developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): one of the three spots obtained from the sample solution and the spot obtained from the standard solution show the same *R*f value.

(2) To an amount of powdered Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, equivalent to 30 mg of Phenobarbital, add 10 mL of ethanol (95), shake, filter, and use the filtrate as the sample solution. Separately, dissolve 30 mg of phenobarbital for assay in 10 mL of ethanol (95), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethylamine (50:1) to a distance of about 10 cm, and air-dry the plate. Again, develop the plate with the same developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): one of the three spots obtained from the sample solution and the spot obtained from the standard solution show the same *R*f value.

(3) To an amount of powdered Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, equivalent to 12.5 mg of Promethazine Hydrochloride, add 10 mL of ethanol (95), shake, filter, and use the filtrate as the sample solution. Separately, dissolve 12.5 mg of promethazine hydrochloride for thin-layer chromatography in 10 mL of ethanol (95), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 5 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethylamine (50:1) to a distance of about 10 cm, and air-dry the plate. Again, develop the plate with the same developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): one of the three spots obtained from the sample solution and the spot obtained from the standard solution show the same *R*f value.

Uniformity of dosage units *<6.02>* Perform the test according to the following method: it meets the requirement of the Content uniformity test. Conduct this procedure using light-resistant vessels.

(1) Chlorpromazine Hydrochloride－To 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20 minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet *V* mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly *V'* mL so that each mL contains about 12.5 μg of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S.HCl$), centrifuge, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay (1).

Amount (mg) of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S.HCl$)
$= M_S \times A_T / A_S \times V' / V \times 1/20$

M_S: Amount (mg) of chlorpromazine hydrochloride for assay taken

(2) Phenobarbital－To 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20

minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet *V* mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly *V'* mL so that each mL contains about 30 μg of phenobarbital ($C_{12}H_{12}N_2O_3$), centrifuge, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay (2).

Amount (mg) of phenobarbital ($C_{12}H_{12}N_2O_3$)
$= M_S \times A_T / A_S \times V' / V \times 1 / 10$

M_S: Amount (mg) of phenobarbital for assay taken

(3) Promethazine Hydrochloride－To 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20 minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet *V* mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly *V'* mL so that each mL contains about 12.5 μg of promethazine hydrochloride ($C_{17}H_{20}N_2S$.HCl), centrifuge, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay (3).

Amount (mg) of promethazine hydrochloride ($C_{17}H_{20}N_2S$.HCl)
$= M_S \times A_T / A_S \times V' / V \times 1 / 20$

M_S: Amount (mg) of promethazine hydrochloride for assay taken

Dissolution *<6.10>* **(1)** Chlorpromazine hydrochloride－When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution (pH 4.0) as the dissolution medium, the dissolution rate in 90 minutes of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets is not less than 75%.

Start the test with 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 14 μg of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S$.HCl), and use this solution as the sample solution. Separately, weigh accurately about 14 mg of chlorpromazine hydrochloride for assay, previously dried at 105℃ for 2 hours, dissolve in methanol to make exactly 50 mL, and use this solution as the chlorpromazine hydrochloride standard stock solution. Pipet 5 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of chlorpromazine in each solution.

Dissolution rate (%) with respect to the labeled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S$.HCl)
$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$

M_S: Amount (mg) of chlorpromazine hydrochloride for assay taken

C: Labeled amount (mg) of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S$.HCl) in 1 tablet

Operating conditions－

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase: Dissolve 3.9 g of sodium dihydrogen phosphate dihydrate in water to make 1000 mL. To 810 mL of this solution add 390 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of chlorpromazine is about 13 minutes.

System suitability－

System performance: To 5 mL of the chlorpromazine hydrochloride standard stock solution add 5 mL each of the phenobarbital standard stock solution obtained in (2) and promethazine hydrochloride standard stock solution obtained in (3), then add the dissolution medium to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order and the resolutions between the peaks of phenobarbital and promethazine and between the peaks of promethazine and chlorpromazine are not less than 6, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of chlorpromazine is not more than 2.0%.

(2) Phenobarbital－When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution (pH 4.0) as the dissolution medium, the dissolution rate in 90 minutes of Chlorpromazine Hydrochloride, Phe-

nobarbital and Promethazine Hydrochloride Tablets is not less than 70%.

Start the test with 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 33 μg of phenobarbital ($C_{12}H_{12}N_2O_3$), and use this solution as the sample solution. Separately, weigh accurately about 33 mg of phenobarbital for assay, previously dried at 105℃ for 2 hours, dissolve in methanol to make exactly 50 mL, and use this solution as the phenobarbital standard stock solution. Pipet 5 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of phenobarbital in each solution.

Dissolution rate (%) with respect to the labeled amount of phenobarbital ($C_{12}H_{12}N_2O_3$)

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 90$

M_S: Amount (mg) of phenobarbital for assay taken

C: Labeled amount (mg) of phenobarbital ($C_{12}H_{12}N_2O_3$) in 1 tablet

Operating conditions —

Proceed as directed in the operating conditions in (1).

System suitability —

System performance: To 5 mL of the phenobarbital standard stock solution add 5 mL each of chlorpromazine hydrochloride standard stock solution obtained in (1) and promethazine hydrochloride standard stock solution obtained in (3), then add the dissolution medium to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order and the resolutions between the peaks of phenobarbital and promethazine and between the peaks of promethazine and chlorpromazine are not less than 6, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of phenobarbital is not more than 2.0%.

(3) Promethazine hydrochloride—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution (pH 4.0) as the dissolution medium, the dissolution rate in 90 minutes of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets is not less than 75%.

Start the test with 1 tablet of Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 14 μg of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$), and use this solution as the sample solution. Separately, weigh accurately about 14 mg of promethazine hydrochloride for assay, previously dried at 105℃ for 3 hours, dissolve in methanol to make exactly 50 mL, and use this solution as the promethazine hydrochloride standard stock solution. Pipet 5 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of promethazine in each solution.

Dissolution rate (%) with respect to the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$)

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 90$

M_S: Amount (mg) of promethazine hydrochloride for assay taken

C: Labeled amount (mg) of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$) in 1 tablet

Operating conditions —

Proceed as directed in the operating conditions in (1).

System suitability —

System performance: To 5 mL of the promethazine hydrochloride standard stock solution add 5 mL each of chlorpromazine hydrochloride standard stock solution obtained in (1) and phenobarbital standard stock solution obtained in (2), then add the dissolution medium to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order and the resolutions between the peaks of phenobarbital and promethazine and between the peaks of promethazine and chlorpromazine are not less than 6, respectively.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of promethazine is not more than 2.0%.

Assay Conduct this procedure using light-resistant vessels.

(1) Chlorpromazine hydrochloride－Weigh accurately the mass of not less than 20 Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 12.5 mg of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S.HCl$), add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20 minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet 5 mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 25 mg of chlorpromazine hydrochloride for assay, previously dried at 105℃ for 2 hours, dissolve in a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 200 mL, and use this solution as the chlorpromazine hydrochloride standard stock solution. Pipet 5 mL of this solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of chlorpromazine in each solution.

Amount (mg) of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S.HCl$) $= M_S \times A_T / A_S \times 1/2$

M_S: Amount (mg) of chlorpromazine hydrochloride for assay taken

Operating conditions －

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase: Dissolve 3.9 g of sodium dihydrogen phosphate dihydrate in water to make 1000 mL. To 810 mL of this solution add 390 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of chlorpromazine is about 11 minutes.

System suitability －

System performance: To 5 mL of the chlorpromazine hydrochloride standard stock solution add 5 mL each of the phenobarbital standard stock solution prepared in (2) and the promethazine hydrochloride standard stock solution prepared in (3), and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order, and the resolutions between the peaks of phenobarbital and promethazine is not less than 5, and that between the peaks of promethazine and chlorpromazine is not less than 9.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of chlorpromazine is not more than 1.0%.

(2) Phenobarbital－Weigh accurately the mass of not less than 20 Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 30 mg of phenobarbital ($C_{12}H_{12}N_2O_3$), add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20 minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet 5 mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 30 mg of phenobarbital for assay, previously dried at 105℃ for 2 hours, dissolve in a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL, and use this solution as the phenobarbital standard stock solution. Pipet 5 mL of this solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of phenobarbital in each solution.

Amount (mg) of phenobarbital ($C_{12}H_{12}N_2O_3$) $= M_S \times A_T / A_S$

M_S: Amount (mg) of phenobarbital for assay taken

Operating conditions －

Proceed as directed in the operating conditions in (1).

System suitability －

System performance: To 5 mL of the phenobarbital standard stock solution add 5 mL each of the chlorpromazine hydrochloride standard stock solution prepared in (1) and the promethazine hydrochloride standard stock solution prepared in (3), and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make 50 mL. When the procedure is run with 10 μL of this

solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order, and the resolutions between the peaks of phenobarbital and promethazine is not less than 5, and that between the peaks of promethazine and chlorpromazine is not less than 9.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of phenobarbital is not more than 1.0%.

(3) Promethazine hydrochloride－Weigh accurately the mass of not less than 20 Chlorpromazine Hydrochloride, Phenobarbital and Promethazine Hydrochloride Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 12.5 mg of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$), add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1), shake vigorously for 20 minutes, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 100 mL. Pipet 5 mL of the solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 25 mg of promethazine hydrochloride for assay, previously dried at 105℃ for 3 hours, dissolve in a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 200 mL, and use this solution as the promethazine hydrochloride standard stock solution. Pipet 5 mL of this solution, add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of promethazine in each solution.

Amount (mg) of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$)
$= M_S \times A_T / A_S \times 1/2$

M_S: Amount (mg) of promethazine hydrochloride for assay taken

Operating conditions－

Proceed as directed in the operating conditions in (1).

System suitability－

System performance: To 5 mL of the promethazine hydrochloride standard stock solution add 5 mL each of the chlorpromazine hydrochloride standard stock solution prepared in (1) and the phenobarbital standard stock solution prepared in (2), and add a mixture of diluted phosphoric acid (1 in 500) and ethanol (99.5) (1:1) to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, phenobarbital, promethazine and chlorpromazine are eluted in this order, and the resolutions between the peaks of phenobarbital and promethazine is not less than 5, and that between the peaks of promethazine and chlorpromazine is not less than 9.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of promethazine is not more than 1.0%.

Containers and storage Containers－Well-closed containers.

Add the following to 9.41 Reagents, Test Solutions:

Promethazine hydrochloride for assay $C_{17}H_{20}N_2S.HCl$ [Same as the monograph Promethazine Hydrochloride. When dried, it contains not less than 99.0% of promethazine hydrochloride ($C_{17}H_{20}N_2S.HCl$).]

Promethazine hydrochloride for thin-layer chromatography $C_{17}H_{20}N_2S.HCl$ [Same as the monograph Promethazine Hydrochloride]