Telmisartan and Amlodipine Besilate Tablets

テルミサルタン・アムロジピンベシル酸塩錠

Telmisartan and Amlodipine Besilate Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$: 514.62) and amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$: 567.05)

Method of preparation Prepare as directed under Tablets, with Telmisartan and Amlodipine Besilate.

Identification (1) Perform the test with 5 μL each of the sample solution and standard solution obtained in the Assay (1) as directed under Liquid Chromatography *<2.01>* according to the following conditions: the retention times of the peaks of telmisartan in the chromatograms obtained from the sample solution and the standard solution are the same, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions －

Column, column temperature, mobile phase A, mobile phase B, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).

Detector: A photodiode array detector (wavelength: 270 nm; measuring range of spectrum: 210 – 400 nm).

System suitability －

System performance: Proceed as directed in the system suitability in the Assay (1).

(2) Perform the test with 5 μL each of the sample solution and standard solution obtained in the Assay (2) as directed under Liquid Chromatography *<2.01>* according to the following conditions: the retention times of the peaks of amlodipine besilate in the chromatograms obtained from the sample solution and the standard solution are the same, and both spectra of these peaks in the chromatograms exhibit similar intensities of absorption at the same wavelengths.

Operating conditions －

Column, column temperature, mobile phase A, mobile phase B, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (2).

Detector: A photodiode array detector (wavelength: 237 nm; measuring range of spectrum: 210 – 400 nm).

System suitability －

System performance: Proceed as directed in the system suitability in the Assay (2).

Uniformity of dosage unit *<6.02>* Perform the test according to the following method: it meets the requirement of the Content uniformity test.

(1) Telmisartan－To 1 tablet of Telmisartan and Amlodipine Besilate Tablets add 4/5V mL of the dissolving solution, disintegrate by sonicating, and add the dissolving solution to make exactly V mL so that each mL contains about 1.6 mg of telmisartan ($C_{33}H_{30}N_4O_2$). Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Then, proceed as directed in the Assay (1).

$$\text{Amount (mg) of telmisartan } (C_{33}H_{30}N_4O_2) = M_S \times A_T / A_S \times V / 50$$

M_S: Amount (mg) of telmisartan for assay taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

(2) Amlodipine Besilate－To 1 tablet of Telmisartan and Amlodipine Besilate Tablets add 4/5V mL of the dissolving solution, disintegrate by sonicating, and add the dissolving solution to make exactly V mL so that each mL contains about 0.138 mg of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$). Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Then, proceed as directed in the Assay (2).

$$\text{Amount (mg) of amlodipine besilate } (C_{20}H_{25}ClN_2O_5.C_6H_6O_3S) = M_S \times A_T / A_S \times V / 250$$

M_S: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Dissolution *<6.10>* **(1)** Telmisartan－When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 30 minutes of a telmisartan 40-mg and amlodipine besilate 6.93-mg tablet is not less than 80%, and that in 45 minutes of a telmisartan 80-mg and amlodipine besilate 6.93-mg tablet is not less than 80%.

Start the test with 1 tablet of Telmisartan and Amlodipine Besilate 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 5 mL or more 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 44 μg of telmisartan ($C_{33}H_{30}N_4O_2$), and use this solution as the sample solution. Separately, weigh accurately about 44 mg of telmisartan for assay, previously dried at 105℃ for 4 hours, dissolve in 10 mL of a solution of meglumine in methanol (1 in 250), and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 25 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 telmisartan in each solution.

Dissolution rate (%) with respect to the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$)

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

M_S: Amount (mg) of telmisartan for assay taken

C: Labeled amount (mg) of telmisartan ($C_{33}H_{30}N_4O_2$) in 1 tablet

Operating Conditions —

Detector, column, column temperature, mobile phase A, mobile phase B, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).

System suitability —

System performance: When the procedure is run with 25 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of telmisartan are not less than 25,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 25 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 2.0%.

(2) Amlodipine Besilate — When the test is performed at 75 revolutions per minute according to the Basket method, using 900 mL of 1st fluid for dissolution test as the dissolution medium, the dissolution rate in 30 minutes of a telmisartan 40-mg and amlodipine besilate 6.93-mg tablet is not less than 75%, and that in 45 minutes of a telmisartan 80-mg and amlodipine besilate 6.93-mg tablet is not less than 80%.

Start the test with 1 tablet of Telmisartan and Amlodipine Besilate 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 5 mL or more of the filtrate, pipet *V* mL of the subsequent filtrate, and add the dissolution medium to make exactly *V'* mL so that each mL contains about 7.7 μg of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$). Pipet 2 mL of this solution, add exactly 2 mL of methanol, and use this solution as the sample solution. Separately, weigh accurately about 7.5 mg of Amlodipine Besilate RS (separately determine the water <*2.48*> in the same manner as Amlodipine Besilate), and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution, and add the dissolution medium to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL of methanol, and use this solution as the standard solution. Perform the test with exactly 50 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 amlodipine in each solution.

Dissolution rate (%) with respect to the labeled amount of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$)

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

M_S: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

C: Labeled amount (mg) of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$) in 1 tablet

Operating Conditions —

Detector, column, column temperature, mobile phase A, mobile phase B, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (2).

System suitability —

System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of amlodipine are not less than 25,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of amlodipine is not more than 2.0%.

Assay (1) Telmisartan — Weigh accurately the mass of not less than 20 Telmisartan and Amlodipine Besilate Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 80 mg of telmisartan ($C_{33}H_{30}N_4O_2$), add 40 mL of the dissolving solution, disintegrate by sonicating, and add the dissolving solution to make exactly 50 mL. Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 80 mg of telmisartan for assay, previously

dried at 105℃ for 4 hours, add the dissolving solution to make exactly 50 mL, and use this solution as the telmisartan standard stock solution. Pipet 5 mL of the telmisartan standard stock solution, add the buffer solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 5 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 telmisartan in each solution.

Amount (mg) of telmisartan ($C_{33}H_{30}N_4O_2$)
$= M_S \times A_T / A_S$

M_S: Amount (mg) of telmisartan for assay taken

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 7.5 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.

Mobile phase B: Acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2.0	90	10
2.0 – 7.0	90 → 20	10 → 80
7.0 – 8.0	20	80

Flow rate: 0.8 mL per minute.

System suitability —

System performance: To each 5 mL of the telmisartan standard stock solution and the amlodipine besilate standard stock solution obtained in (2) add the buffer solution to make 25 mL. When the procedure is run with 5 μL of this solution under the above operating conditions, amlodipine and telmisartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 1.0%.

(2) Amlodipine Besilate — Weigh accurately the mass of not less than 20 Telmisartan and Amlodipine Besilate Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 6.9 mg of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$), add 40 mL of the dissolving solution, disintegrate by sonicating, and add the dissolving solution to make exactly 50 mL. Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Separately, weigh accurately about 35 mg of Amlodipine Besilate RS (separately determine the water <2.48> in the same manner as Amlodipine Besilate) and add the dissolving solution to make exactly 100 mL. Pipet 20 mL of this solution, add the dissolving solution to make exactly 50 mL, and use this solution as the amlodipine besilate standard stock solution. Pipet 5 mL of the amlodipine besilate standard stock solution, add the buffer solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 5 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 amlodipine in each solution.

Amount (mg) of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$)
$= M_S \times A_T / A_S \times 1/5$

M_S: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 237 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 7.5 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.

Mobile phase B: Acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2.0	90	10
2.0 – 7.0	90 → 20	10 → 80
7.0 – 8.0	20	80

Flow rate: 0.8 mL per minute.

System suitability —

System performance: To 5 mL each of the telmisartan standard stock solution obtained in (1) and the amlodipine besilate standard stock solution add the buffer solution to make 25 mL. When the procedure is run with 5 μL of this solution under the above operating conditions, amlodipine and telmisartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 1.0%.

Containers and storage Containers — Tight containers.