Montelukast Sodium Granules

モンテルカストナトリウム顆粒

Montelukast Sodium Granules contain not less than 95.0% and not more than 105.0% of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$: 586.18).

Method of preparation Prepare as directed under Granules, with Montelukast Sodium.

Identification To an amount of Montelukast Sodium Granules, equivalent to 5 mg of montelukast ($C_{35}H_{36}ClNO_3S$), add 500 mL of a mixture of methanol and water (3:1), shake, and centrifuge. Determine the absorption spectrum of the supernatant liquid as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits maxima between 281 nm and 285 nm, between 325 nm and 329 nm, between 343 nm and 347 nm, and between 357 nm and 361 nm.

Purity Related substances－Use the sample solution obtained in the Assay as the sample solution. Pipet 1 mL of the sample solution, add a mixture of methanol and water (3:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine each peak area by the automatic integration method: the total area of the two peaks of related substance A, having the relative retention time of about 0.45 to montelukast, obtained from the sample solution is not larger than the peak area of montelukast obtained from the standard solution, and the peak area of related substance B, having the relative retention time of about 0.92 to montelukast, from the sample solution is not larger than 3/20 times the peak area of montelukast from the standard solution, and the area of the peak other than montelukast and the peaks mentioned above from the sample solution is not larger than 1/10 times the peak area of montelukast from the standard solution. Furthermore, the total area of the peaks other than montelukast from the sample solution is not larger than 1.2 times the peak area of montelukast from the standard solution. However, the peaks of the related substances derived from Montelukast Sodium [having the relative retention time of about 1.04 (related substance E), about 1.16 (related substance C), about 1.18 (related substance D), about 1.24 and about 1.55 (related substance F) to montelukast] are excluded. For the area of the peak, having the relative retention time of about 0.71 to montelukast, multiply the relative response factor 0.6.

Operating conditions－

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 1.5 times as long as the retention time of montelukast, beginning after the solvent peak.

System suitability—

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

Test for required detectability: Pipet 10 mL of the standard solution, and add a mixture of methanol and water (3:1) to make exactly 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of montelukast is not less than 10.

System repeatability: When the test is repeated 5 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of montelukast is not more than 2.0%.

Uniformity of dosage unit *<6.02>* Perform the test according to the following method: Montelukast Sodium Granules in single-dose packages meet the requirement of the Content uniformity test.

Conduct this procedure using light-resistant vessels. To the total content of 1 package of Montelukast Sodium Granules add 130 mL of methanol, disperse the fine particles by sonicating, and add methanol to make exactly V mL so that each mL contains about 20 μg of montelukast ($C_{35}H_{36}ClNO_3S$). Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 33 mg of Montelukast Dicyclohexylamine RS, and dissolve in methanol to make exactly 100 mL. Pipet 8 mL of this solution, add methanol to make exactly 100 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 montelukast in each solution.

$$\text{Amount (mg) of montelukast } (C_{35}H_{36}ClNO_3S) = M_S \times A_T / A_S \times V / 1250 \times 0.764$$

M_S: Amount (mg) of Montelukast Dicyclohexylamine RS taken

Operating conditions－

Detector: An ultraviolet absorption photometer (wavelength: 389 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 10 cm in length, packed with phenylated silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50℃.

Mobile phase: A solution of trifluoroacetic acid in a mixture of water and acetonitrile for liquid chromatography (1:1) (1 in 500).

Flow rate: Adjust so that the retention time of montelukast is about 2 minutes.

System suitability－

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of montelukast are not less than 1500 and not more than 1.5, respectively.

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

Dissolution *<6.10>* When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of a solution of sodium lauryl sulfate (1 in 200) as the dissolution medium, the dissolution rate in 15 minutes of Montelukast Sodium Granules is not less than 85%.

Conduct this procedure using light-resistant vessels. Start the test with an accurately weighed amount of Montelukast Sodium Granules, equivalent to about 4 mg of montelukast ($C_{35}H_{36}ClNO_3S$), withdraw not less than 15 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, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 27 mg of Montelukast Dicyclohexylamine RS, and dissolve in methanol to make exactly 100 mL. Pipet 2 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 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 montelukast in each solution.

Dissolution rate (%) with respect to the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$)

$$= M_S / M_T \times A_T / A_S \times 1 / C \times 18 \times 0.764$$

M_S: Amount (mg) of Montelukast Dicyclohexylamine RS taken
M_T: Amount (g) of Montelukast Sodium Granules taken
C: Labeled amount (mg) of montelukast ($C_{35}H_{36}ClNO_3S$) in 1 g

Operating Conditions—
Proceed as directed in the operating conditions in the Uniformity of dosage units.

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 montelukast are not less than 2000 and not more than 1.5, 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 montelukast is not more than 1.0%.

Assay Conduct this procedure using light-resistant vessels. Weigh accurately an amount of Montelukast Sodium Granules, equivalent to about 60 mg of montelukast ($C_{35}H_{36}ClNO_3S$), and add a mixture of methanol and water (3:1) to make exactly 250 mL. Disperse the fine particles by sonicating, centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 33 mg of Montelukast Dicyclohexylamine RS, and dissolve in a mixture of methanol and water (3:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 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 montelukast in each solution.

Amount (mg) of montelukast ($C_{35}H_{36}ClNO_3S$)

$$= M_S \times A_T / A_S \times 5 / 2 \times 0.764$$

M_S: Amount (mg) of Montelukast Dicyclohexylamine RS taken

Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 255 nm).
Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with phenylhexylsilanized silica gel for liquid chromatography (3 μm in particle diameter).
Column temperature: A constant temperature of about 50℃.
Mobile phase A: A solution of trifluoroacetic acid (1 in 500).
Mobile phase B: A mixture of methanol and acetonitrile for liquid chromatography (3:2).
Flowing of mobile phase: Control the gradient by mixing the mobile phase A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 — 5	48 → 45	52 → 55
5 — 12	45	55
12 — 22	45 → 25	55 → 75
22 — 23	25	75

Flow rate: 1.5 mL per minute (the retention time of montelukast is about 14 minutes).

System suitability—
System performance: Take 10 mL of the standard solution in a transparent vessel, add 4 μL of hydrogen peroxide (30), and allow to stand under 4000 lx white light for 10 minutes. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the peak of related substance B, having the relative retention time of about 0.92 to montelukast, and the peak of montelukast is not less than 1.5. And proceed with 20 μL of the standard solution under the above operating conditions, the number of the theoretical plates and the symmetry factor of the peak of montelukast are not less than 5000 and not more than 2.5, respectively.

System repeatability: When the test is repeated 5 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of montelukast is not more than 1.0%.

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Others
Related substances A, B, C, D, E and F: Refer to them described in Montelukast Sodium.