Misoprostol dispersion (Misoprostoli dispersio)

2016-01

Description. A white or almost white powder.

Category. Prostaglandin (PGE_1) analogue.

Storage. Misoprostol is hygroscopic, misoprostol dispersion it should be stored below 8 °C under nitrogen in sealed containers, protected from light, and should not be exposed to moisture.

Requirements

Definition. Misoprostol dispersion is a mixture of Misoprostol and Hypromellose. It contains not less than 95.0% and not more than 105.0% of the amount of $C_{22}H_{38}O_5$ stated on the label.

Identity tests

-Either tests A and C or tests B and C may be applied.

A. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).

B. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 µL of each of the following two solutions in dehydrated ethanol R. For solution (1) shake mechanically a quantity of the dispersion equivalent to 1 mg of misoprostol with 10.0 mL of dehydrated ethanol R for 10 minutes, filter and use the clear filtrate. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).

C. Carry out test C1, C2 and C3.

C1. Evenly distribute 1.0 g of the dispersion into 100 mL of boiling water R, and stir the mixture using a magnetic stirrer with a bar 25 mm long: a slurry is formed and the particles do not dissolve. Allow the slurry to cool to 10 °C and stir using a magnetic stirrer: a mucilaginous colloidal mixture occurs with its thickness dependent on the viscosity grade of the Hypromellose.

C2. To 0.1 mL of the mixture obtained in identification test C1 add 9 mL of sulfuric acid (90% v/v) TS, shake, heat on a water-bath for exactly 3 min, immediately cool in an ice-bath, carefully add 0.6 mL of a 20 g/L solution of ninhydrin R, shake and allow to stand at 25 °C: a red colour develops at first and changes to purple within 100 minutes.

C3. Pour 2–3 ml of the mixture prepared for identity test C1 onto a glass plate as a thin film and allow the water to evaporate. A coherent, self-sustaining film is formed.

Loss on drying. Dry about 300 mg of the dispersion at 105 °C for 2 hours; it loses not more than 15 mg/g.

Related substances

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under *1.14.4 High performance liquid chromatography* using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 µm).

Use the following conditions for gradient elution:

mobile phase A: mix 28 volumes of acetonitrile for chromatography R with 69 volumes of water R and 3 volumes of methanol for chromatography R;

mobile phase B: mix 47 volumes of acetonitrile for chromatography R with 50 volumes of water R and 3 volumes of methanol chromatography R.

Time (minutes)	Mobile phase A	Mobile phase B	Comment

	(% v/v)	(% v/v)	
0–5	100	0	isocratic
5–15	100 to 65	0 to 35	linear gradient
15–(t_r + 1)	65	35	isocratic
(t_r + 1)–(t_r + 4)	65 to 0	35 to 100	linear gradient
(t_r + 4)–(t_r + 9)	0	100	isocratic
(t_r + 9)–(t_r + 11)	0 to 100	100 to 0	linear gradient
(t_r + 11)–(t_r + 19)	100	0	re-equilibration

t_r = retention time of misoprostol determined with solution (1)

Maintain the column temperature at 35 °C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water as solvent. For solution (1) mix a quantity of the dispersion equivalent to about 8 mg of misoprostol, accurately weighed, with 20.0 mL of acetonitrile R and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Centrifuge and filter the supernatant. Evaporate 8.0 mL of the filtrate to dryness under a stream of nitrogen, dissolve the residue in 4.0 mL of solvent, using a vortex mixer. For solution (2) dilute 1 volume of solution (1) to 500 volumes. For solution (3) heat 2 mL of solution (1) in a water bath at 75 °C for 1 hour.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm.

Inject 100 µL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes)) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol.

Inject alternately 100 µL each of solutions (1) and (2).

The chromatogram obtained with solution (1) may show the following impurities at the following relative retentions with reference to misoprostol (retention time about 21 minutes): impurity E (1st peak): about 0.84; impurity E (2nd peak): about 0.86; impurity B (1st peak): about 0.90; impurity B (2nd peak): about 0.92; impurity A: about 0.95; impurity D: about 1.27; impurity C: about 1.37. Use also the chromatogram obtained with solution (3) to identify impurity A and C.

In the chromatogram obtained with solution (1):

- -the sum of the areas of any peak corresponding to impurity A, B and E is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- -the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
- -the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- -the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than 12.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Diastereoisomers

Carry out the test as described under *1.14.4 High performance liquid chromatography* using a stainless steel column (15 cm × 2.1 mm) packed with hybrid organic silica gel for chromatography R (3.5 µm). As the mobile phase use a mixture of 4 volumes of 2-propanol R, 96 volumes of heptane R and 0.1 volume of trifluoroacetic acid R.

Prepare the following test solution using as a solvent a mixture of 4 volumes of 2-propanol R and 96 volumes of heptane R. Mix a quantity of the disperison equivalent to about 2 mg of misoprostol with 5.0 mL of acetonitrile R and sonicate for 10 minutes ensuring that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Centrifuge and filter the supernatant. Evaporate 2.0 mL of the filtrate to dryness with nitrogen, dissolve the residue in 1.0 mL of solvent and vortex for 1 minute.

Maintain the column temperature at 25 °C.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 205 nm. Store the samples at 4 °C during analysis, using a cooled autosampler.

Inject 10 µL of the test solution.

The chromatogram shows two principal peaks due to misoprostol at retention times of about 14 and 16 minutes. The test is not valid unless the resolution between these two peaks is at least 2.0.

Measure the areas of the two peaks corresponding to misoprostol. The first peak of misoprostol is 45% to 55% of the sum of the areas of the two peaks due to misoprostol.

Assay

Carry out the test as described under *1.14.4 High performance liquid chromatography* using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 µm). As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water.

Prepare the following solutions in the mobile phase. For solution (1) mix a quantity of the dispersion equivalent to about 4 mg of misoprostol, accurately weighed, with 200.0 mL of mobile phase and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Filter a portion of this solution, discarding the first few mL of the filtrate. For solution (B) use 20 µg of misoprostol RS per mL.

Maintain the column temperature at 35 °C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4 °C during analysis, using a cooled autosampler.

Inject alternately 100 µL each of solutions (1) and (2). The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of misoprostol ($C_{22}H_{38}O_5$) in the dispersion, using the declared content of $C_{22}H_{38}O_5$ in misoprostol RS.

Impurities

The impurities limited by the requirements of this monograph are those listed in the monograph for Misoprostol.