Misoprostol tablets (Misoprostoli compressi)

2016-01

Category. Prostaglandin (PGE_1), analogue.

Storage. Misoprostol tablets should be kept in tightly closed containers, protected from humidity.

Additional information. Strength in the current WHO Model List of Essential Medicines: 100 µg, 200 µg.

Requirements

Comply with the monograph for *Tablets*.

Misoprostol tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{22}H_{38}O_5$ stated on the label.

Identity tests

Either test A or B 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 powdered tablets equivalent to 1 mg of misoprostol with 10 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).

Dissolution. Carry out the test as described under *5.5 Dissolution test for solid oral dosage forms* using as the dissolution medium 500 mL of water R and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature (solution (A)). For solution (B) dilute a suitable volume of solution (2) described under "Assay" with water R to obtain a concentration of 0.2 µg of misoprostol per mL for 100 µg tablets and 0.4 µg of misoprostol per mL for 200 µg tablets.

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the method described under "Assay". Inject 250 µL each of solutions (A) and (B) and measure the areas of the peak responses corresponding to misoprostol obtained in the chromatograms.

For each of the tablets tested calculate the total amount of misoprostol ($C_{22}H_{38}O_5$) in the medium from the peak areas obtained using the declared content of $C_{22}H_{38}O_5$ in misoprostol RS. Use the requirements as described under *5.5 Dissolution test for solid oral dosage forms*, Acceptance criteria to evaluate the results: the amount in solution is not less than 80% (Q) of the amount declared on the label.

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 for chromatography R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0–5	100	0	isocratic

5–15	100 to 65	0 to 35	linear gradient
15–(t_r + 1) 22	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 R as solvent. For solution (1) weigh and powder 20 tablets, mix a quantity of the powder equivalent to about 2000 µg of misoprostol, accurately weighed, with 10.0 mL of acetonitrile R and sonicate for about 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 6.0 mL of the filtrate to dryness under a stream of nitrogen and dissolve the residue in 3.0 mL of solvent, using a vortex mixer. For solution (2) dilute 1 volume of solution (1) to 200 volumes. For solution (3) heat 1 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 200 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 200 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 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);
- -the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);
- -the area of any peak corresponding to impurity D is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Assay

-Either method A or B may be applied.

A. 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 R.

Prepare the following solutions in the mobile phase. For solution (1) weigh and powder 20 tablets, weigh accurately a quantity of the powder equivalent to about 400 µg of misoprostol in a 20.0 mL volumetric flask. Add about 10 mL and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol and make up to volume. Filter a portion of this solution, discarding the first few mL of the filtrate. For solution (2) 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 tablets, using the declared content of $C_{22}H_{38}O_5$ in misoprostol RS.

B. Use the average of the 10 individual results obtained in the test for “Uniformity of content”.

Uniformity of content

The tablets comply with the test for *5.1 Uniformity of content for single-dose preparations* using the following method of analysis.

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the chromatographic conditions as described under “Assay”, method A.

Prepare the following solutions using the mobile phase as diluent.

For 100 µg tablets: For solution (1) transfer one tablet to a 5 mL volumetric flask. Add about 3 mL and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol and make up to volume. Filter a portion of this solution, discarding the first few mL of the filtrate. *For 200 µg tablets*: For solution (1) transfer one tablet to a 10 mL volumetric flask. Add about 6 mL and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol and make up to volume. Filter a portion of this solution, discarding the first few mL of the filtrate.

For solution (2) use 20 µg of misoprostol RS per mL.

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 each tablet, 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.