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Clopidogrel Hydrogen Sulfate Tablets

General Notices

Clopidogrel Bisulfate Tablets

Action and use

Inhibitor of ADP-mediated platelet aggregation; antiplatelet.

DEFINITION

Clopidogrel Hydrogen Sulfate Tablets contain Clopidogrel Hydrogen Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of clopidogrel, $C_{16}H_{16}ClNO_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered tablets containing the equivalent of 50 mg of clopidogrel with 10 mL of *anhydrous ethanol*, filter and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of clopidogrel hydrogen sulfate *(RS 516)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of a solution containing 12 volumes of 0.1M *hydrochloric acid* and 88 volumes of 0.657% w/v of *potassium chloride*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* at 240 nm of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.008% w/v of clopidogrel, Appendix II B, using dissolution medium in the reference cell.
(2) Measure the *absorbance* at 240 nm of a 0.011% w/v solution of *clopidogrel hydrogen sulfate BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of clopidogrel, $C_{16}H_{16}ClNO_2S$, in the medium from the absorbances obtained and using the declared content of $C_{16}H_{16}ClNO_2S,H_2SO_4$ in *clopidogrel hydrogen sulfate BPCRS*.

Each mg of $C_{16}H_{16}ClNO_2S,H_2SO_4$ is equivalent to 0.7664 mg of $C_{16}H_{16}ClNO_2S$.

LIMITS

The amount of clopidogrel released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of powdered tablets containing the equivalent of 75 mg of clopidogrel, add 5 mL of *methanol* and mix with the aid of ultrasound. Add 100 mL of the mobile phase and shake. Dilute to produce 200 mL with the mobile phase and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) 0.375% w/v of *clopidogrel for system suitability EPCRS* and 0.00375% w/v of *clopidogrel impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.
(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *protein derivative of silica gel for chiral separation* (5 µm) (Ultron ES-OVM is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 3 times the retention time of clopidogrel.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of 0.01M *potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B (enantiomer 1) and clopidogrel is at least 1.5.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of clopidogrel in solution (2).

For the reporting threshold, use the concentration of clopidogrel in solution (4). Apply the reporting threshold to the sum of impurity B enantiomers 1 and 2.

For peak identification, use solution (3).

Clopidogrel retention time: about 6 minutes.

Relative retention: impurity A, about 0.5; impurity B (enantiomer 1), about 0.8; impurity B (enantiomer 2), about 1.2; impurity C, about 2.0.

LIMITS

— impurity C: not more than 1.5%;

— impurity A: not more than 1.2%;

— impurity B (sum of enantiomers 1 and 2): not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 2.5%;

— reporting threshold: 0.1%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of powdered tablets containing the equivalent of 75 mg of clopidogrel, add 50 mL of *methanol* and mix with the aid of ultrasound. Dilute to produce 100 mL with *methanol*. Dilute 1 volume to 20 volumes with the mobile phase and filter (a 0.45-µm glass microfibre filter is suitable).
(2) 0.1% w/v of *clopidogrel hydrogen sulfate BPCRS* in *methanol*. Dilute 1 volume to 20 volumes with the mobile phase.
(3) 0.375% w/v of *clopidogrel for system suitability EPCRS* and 0.00375% w/v of *clopidogrel impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B (enantiomer 1) and clopidogrel is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of clopidogrel, $C_{16}H_{16}ClNO_2S$, in the tablets from the chromatograms obtained and using the declared content of $C_{16}H_{16}ClNO_2S,H_2SO_4$ in *clopidogrel hydrogen sulfate BPCRS*.

Each mg of $C_{16}H_{16}ClNO_2S,H_2SO_4$ is equivalent to 0.7664 mg of $C_{16}H_{16}ClNO_2S$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of clopidogrel.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Clopidogrel Hydrogen Sulfate.