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Clopidogrel Tablets

» Clopidogrel Tablets contain Clopidogrel Bisulfate equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clopidogrel ($C_{16}H_{16}ClNO_2S$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—

USP Clopidogrel Bisulfate RS

USP Clopidogrel Related Compound A RS
(+)-(*S*)-(*o*-Chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetic acid.

USP Clopidogrel Related Compound B RS
Methyl (±)-(*o*-chlorophenyl)-4,5-dihydrothieno[2,3-*c*]pyridine-6(7*H*)-acetate, hydrochloride.

USP Clopidogrel Related Compound C RS
Methyl (−)-(*R*)-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate, hydrogen sulfate.

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests ⟨197⟩, Ultraviolet-Visible Spectroscopy: 197U*▲ (CN 1-May-2020) —

Spectral range: 250 to 300 nm.

Solution—Use the test solution prepared as directed in the test for *Uniformity of dosage units*.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Dissolution ⟨711⟩—

Medium: pH 2.0 hydrochloric acid buffer (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*); 1000 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Clopidogrel Bisulfate RS in 20.0 mL of methanol, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration corresponding to that of the solution under test.

Procedure—Determine the amount of $C_{16}H_{16}ClNO_2S$ dissolved by employing UV absorption at a wavelength of about 240 nm on filtered portions of the solution under test in comparison with the *Standard solution*.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{16}ClNO_2S$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Procedure for content uniformity—Using a suitable volumetric flask, place 1 Tablet in 50.0 mL of 0.1 N hydrochloric acid. Sonicate for 5 minutes, and cool. Quantitatively transfer 5.0 mL of this solution to the flask, and dilute with 0.1 N hydrochloric acid to 50.0 mL. Pass a portion of the solution through a suitable filter having a 0.45-µm or finer porosity, discarding the first 5 mL of the filtrate. Determine the amount of clopidogrel by employing UV absorption at the wavelength of maximum absorbance at about 270 nm, in comparison with a Standard solution having a known concentration of USP Clopidogrel Bisulfate RS in 0.1 N hydrochloric acid.

Related compounds—[Note—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]

Phosphate buffer and *Mobile phase*—Prepare as directed in the *Assay* under *Clopidogrel Bisulfate*.

System suitability solution—Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS and USP Clopidogrel Related Compound B RS in methanol, and dilute with methanol to obtain a solution having concentrations of about 100 µg per mL and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution—Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, and USP Clopidogrel Related Compound C RS in methanol to obtain a solution having known concentrations of about 40 µg per mL, 250 µg per mL, and 300 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, and dilute with *Mobile phase* to volume. This

solution contains about 1 µg of clopidogrel bisulfate per mL, 6 µg of clopidogrel related compound A per mL, and 7.5 µg of clopidogrel related compound C per mL.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of clopidogrel (free base), to a 200-mL volumetric flask, add 5 mL of methanol, dilute with *Mobile phase* to volume, and mix. Allow to stand for 10 minutes, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate after discarding the first 5 mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 220-nm detector and 4.6-mm × 15-cm column that contains packing L57. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 and 1.2 for the two enantiomers of clopidogrel related compound B and 1.0 for clopidogrel; and the resolution, *R,* between clopidogrel and the first enantiomer of clopidogrel related compound B is greater than 2.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for clopidogrel related compound A, 1.0 for clopidogrel and 2.0 for clopidogrel related compound C; and the relative standard deviation for replicate injections is not more than 15% for each peak.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of clopidogrel related compounds A and C in the portion of Tablets taken by the formula:

$$20(321.82/419.90)(C/W)(r_U/r_S)$$

in which 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight of clopidogrel bisulfate; C is the concentration, in µg per mL, of the relevant clopidogrel related compound in the *Standard solution; W* is the weight, in mg, of clopidogrel in the portion of Tablets used to prepare the *Test solution* based on the labeled quantity of clopidogrel per Tablet, Tablet weight, and the weight of the portion of Tablets used; and r_U and r_S are the peak responses of the corresponding related compounds obtained from the *Test solution* and the *Standard solution,* respectively.

Calculate the percentage of any other impurity (excluding clopidogrel related compound B) in the portion of Tablets taken by the formula:

$$20(321.82/419.90)(C_C/W)(r_U/r_S)$$

in which C_C is the concentration of clopidogrel bisulfate, in µg per mL, in the *Standard solution;* r_U is the peak response of any other impurity obtained from the *Test solution;* r_S is the peak response of clopidogrel peak obtained from the *Standard solution;* and the other terms are as defined above: not more than 1.2% of clopidogrel related compound A is found, not more than 1.5% of clopidogrel related compound C is found, not more than 0.2% of any other single impurity (excluding clopidogrel related compound B) is found, and not more than 2.5% of total impurities (excluding clopidogrel related compound B) is found.

Assay—[Note—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]

Phosphate buffer, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay* under *Clopidogrel Bisulfate*.

System suitability preparation—Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS and USP Clopidogrel Related Compound B RS in methanol, and quantitatively dilute with methanol to obtain a solution having concentrations of about 100 µg per mL and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Clopidogrel Bisulfate RS in methanol to obtain a solution having a known concentration of about 0.1 mg of clopidogrel bisulfate per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of clopidogrel (base), to a 100-mL volumetric flask, and add 50 mL of methanol. Sonicate for 5 minutes, and stir for 30 minutes. Dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to the flask, dilute with methanol to 50.0 mL, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate after discarding the first 5 mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the analyte peaks. Calculate the quantity, in mg, of clopidogrel ($C_{16}H_{16}ClNO_2S$) in the portion of Tablets taken by the formula:

$$1000(321.82/419.90)C(r_U/r_S)$$

in which 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight of clopidogrel bisulfate; C is the concentration, in mg per mL, of USP Clopidogrel Bisulfate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CLOPIDOGREL TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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