Quinine bisulfate tablets (Quinini bisulfas compressi)

Category. Antimalarial.

Storage. Quinine bisulfate tablets should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines: 300 mg. Strength in the current WHO Model list of essential medicines for children: 300 mg.

300 mg of quinine bisulfate ($7H_2O$) is equivalent to approximately 177.4 mg of anhydrous quinine.

The tablets are coated.

Requirements

Comply with the monograph for "Tablets".

Definition. Quinine bisulfate tablets contain Quinine bisulfate. They contain not less than 90.0% and not more than 110.0% of the amount of quinine bisulfate ($C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$) stated on the label.

Identity tests

• Any two of tests A, B or C may be applied together with tests D and E.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 20 volumes of toluene R, 12 volumes of ether R and 5 volumes of diethylamine R as the mobile phase. Apply separately to the plate 2 µl of each of the following two solutions in a mixture of 2 volumes of chloroform R and 1 volume of ethanol (~750 g/l) TS. For solution (A) shake a quantity of the powdered tablets containing about 0.1 g of Quinine bisulfate with 10 mL, filter, and use the filtrate. If the tablets are sugar coated, remove the coating and powder the tablet cores. For solution (B) use 7 mg of quinine sulfate RS per mL. For solution (C) use 7 mg of quinine sulfate RS and 7 mg of quinidine sulfate RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with sulfuric acid/ethanol (~0.05 mol/l) TS and then with potassium iodobismuthate TS2. Examine the chromatogram in daylight.

The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B. See the test described below under Related cinchona alkaloids. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

C. To a quantity of the powdered tablets containing about 21 mg of Quinine bisulfate add 50 mL of hydrochloric acid (0.1 mol/l) VS, shake and filter. Dilute 5 mL of the filtrate to 50 mL with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 330 nm and 360 nm, exhibits one maximum at about 347 nm.

D. To a quantity of the powdered tablets containing about 0.25 g of Quinine bisulfate add 25 mL of a mixture of 2 volumes of chloroform R and 1 volume of ethanol (~750 g/l) TS, sonicate for about 15 minutes and filter. Evaporate the filtrate to dryness. Stir the residue with 10 mL of ether R and filter. Wash the residue with 10 mL of ether R and dry it at 60°C for 5 hours. The pH of a 10 mg/mL solution of the residue in water R is 2.3 to 4.0.

E. To a quantity of powdered tablets containing 0.1 g of Quinine bisulfate add 10 mL of water R, shake, and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Dissolution/Disintegration

• Either test A or test B may be applied

A. **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 dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 330 nm. At the same time measure the absorbance at the maximum at about 330 nm of a suitable solution of quinine bisulfate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.

For each of the six tablets tested, calculate the total amount of quinine bisulfate ($C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$), in the medium. The amount in solution for each tablet is not less than 80% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

B. **Disintegration.** Comply with 5.3 Disintegration test for tablets and capsules, operating the apparatus for 10 minutes. If the tablets do not comply, carry out test A above.

Related cinchona alkaloids. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm).

As the mobile phase, use a solution prepared as follows: dissolve 6.8 g potassium dihydrogen phosphate R and 3.0 g hexylamine R in 900 mL of water R, adjust to pH 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 mL. Mix 920 mL of this solution with 80 mL of acetonitrile R.

Prepare the following solutions in the solvent consisting of 80 volumes of water R, 20 volumes of acetonitrile R and 0.1 volume of phosphoric acid (~1440 g/l) TS. For solution (1) weigh and powder 20 tablets or, if the tablets are sugar coated, remove the coating and powder the tablet cores. Transfer a quantity of the powder containing about 75 mg of Quinine bisulfate to a 20 mL volumetric flask, add 15 mL of the solvent, sonicate for about 5 minutes, allow to cool to room temperature and make up to volume using the solvent. Filter a portion of this solution through a 0.45 µm filter, discarding the first few mL of the filtrate. For solution (2) dissolve about 30 mg of quinine sulfate RS in 10 mL of the solvent. For solution (3) dissolve about 15 mg of quinidine sulfate RS in 5 mL of solution (2).

Operate with a flow rate of 1.3 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 316 nm.

Inject separately 10 µl each of solutions (1), (2) and (3) in the chromatographic system and record the chromatograms for 2.5 times the retention time of the peak due to quinine (principal peak) obtained with solution (2).

In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to quinine (retention time about 10 minutes): quinidine about 0.8; dihydroquinidine about 1.2; dihydroquinine about 1.5. The test is not valid unless the resolution between the peaks due to quinidine and quinine and that between the peaks due to quinine and dihydroquinidine is at least 1.5. The chromatograms obtained with solutions (1), (2) and (3) may also show a peak due to cinchonidine eluting at a relative retention of about 0.6 with reference to quinine.

Calculate the percentage content of the related substances in the chromatogram obtained with solution (1) by normalization. The content of dihydroquinine is not more than 10%, the content of cinchonidine not more then 5% and the content of any other related substance is not more than 2.5%. The sum of the related substances is not more than 15%. Disregard any related substance of content less than 0.1%.

Assay. Weigh and powder 20 tablets. Gently stir a quantity of the powder containing about 0.40 g of Quinine bisulfate, accurately weighed, in 40 mL of acetic anhydride R for 15 minutes. Titrate with perchloric acid (0.1 mol/l) VS, determine the end point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/l) VS is equivalent to 54.86 mg of quinine bisulfate ($C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Quinine bisulfate.