Quinine Sulfate Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Quinine Sulfate Capsules monograph. The purpose of the revision is to add *Dissolution Test* 2 for a generic product approved by the FDA.

The liquid chromatographic procedure used in the *Dissolution Test* 2 is based on analyses performed with the Phenomenex Luna C18 brand of L1 column. The typical retention time for quinine sulfate and dihydroquinine sulfate are about 5 and 7 minutes respectively.

The Quinine Sulfate Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 40—NF 35*.

Should you have any questions, please contact Praveen Pabba (301–816–8540 or pkp@usp.org).

Quinine Sulfate Capsules

DEFINITION

Quinine Sulfate Capsules contain amounts of quinine sulfate and dihydroquinine sulfate totaling NLT 90.0% and NMT 110.0% of the labeled amount of quinine sulfate, calculated as $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$.

IDENTIFICATION

- **A.**
  Sample: Nominally 100 mg of quinine sulfate from the contents of Capsules
  Analysis: Shake the *Sample* with 100 mL of dilute sulfuric acid (1 in 350), and filter.
  Acceptance criteria: An appropriate dilution of the filtrate exhibits a vivid blue fluorescence. On the addition of a few drops of hydrochloric acid, the fluorescence disappears.
- **B.** The R_F value of the principal spot from the *Sample solution* corresponds to that from *Standard solution A*, as obtained in the test for *Organic Impurities*.
- **C. IDENTIFICATION TESTS—GENERAL ⟨191⟩,** *Chemical Identification Tests, Sulfate*
  Sample: Nominally 20 mg of quinine sulfate from the contents of Capsules
  Analysis: Shake the *Sample* with 10 mL of dilute hydrochloric acid (1 in 100), and filter.
  Acceptance criteria: The filtrate meets the requirements.
- **D.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
  Solution A: Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, and dilute with water to 500 mL.
  Solution B: Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.
  Mobile phase: Acetonitrile, *Solution A*, *Solution B*, and water (100:20:20:860). Adjust with *Solution B* to a pH of 2.6 if the pH is found to be lower.
  System suitability solution: 0.2 mg/mL each of USP Quinine Sulfate RS and dihydroquinine, dissolved in 10% of the final volume of methanol. Dilute with *Mobile phase* to volume.
  Standard solution: 0.2 mg/mL of USP Quinine Sulfate RS in *Mobile phase*
  Sample stock solution: Nominally 1.6 mg/mL of quinine sulfate in methanol prepared as follows. Transfer an amount, equivalent to 160 mg of quinine sulfate from the contents of NLT 20 Capsules, to a 100-mL volumetric flask, add 80 mL of methanol, and shake the flask by mechanical means for 30 min. Dilute with methanol to volume, and filter, discarding the first 10 mL of the filtrate.
  Sample solution: Nominally 0.2 mg/mL of quinine sulfate in *Mobile phase* from the *Sample stock solution*
  Chromatographic system
  (See *Chromatography ⟨621⟩, System Suitability*.)
  Mode: LC
  Detector: UV 235 nm
  Column: 3.9-mm × 30-cm; packing L1
  Flow rate: 1 mL/min
  Injection volume: 50 µL
  System suitability
  Sample: *System suitability solution*
  [NOTE—The relative retention times for quinine and dihydroquinine are 1 and 1.5, respectively.]
  Suitability requirements
  Resolution: NLT 1.2 between quinine and dihydroquinine
  Relative standard deviation: NMT 2.0% for the quinine peak
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ calculated as the sum of quinine sulfate and dihydroquinine sulfate in the portion of Capsules taken:

$$\text{Result} = [(r_{b,U} + r_{d,U})/(r_{b,S} + r_{d,S})] \times (C_S/C_U) \times 100$$

$r_{b,U}$ = peak area response of quinine from the *Sample solution*
$r_{d,U}$ = peak area response of dihydroquinine from the *Sample solution*
$r_{b,S}$ = peak area response of quinine from the *Standard solution*
$r_{d,S}$ = peak area response of dihydroquinine from the *Standard solution*
C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**
  •Test 1• (RB 1-Feb-2017)
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 100 rpm
  Time: 45 min
  Detection: UV maximum at about 248 nm
  Standard solution: Prepare a solution of known concentration of USP Quinine Sulfate RS in *Medium*.
  Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ dissolved.
  Tolerances: NLT 75% (*Q*) of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ is dissolved.
  •Test 2
  If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 100 rpm
  Time: 30 min
  Solution A: Add 7.0 mL of methanesulfonic acid to 4.0 mL of glacial acetic acid, and dilute with water to 100 mL.
  Solution B: Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.
  Mobile phase: Water, acetonitrile, *Solution A*, and *Solution B* (81:15:2:2). Adjust with *Solution B* to a pH of 3.0.
  Standard solution: Prepare a solution of known concentration of USP Quinine Sulfate RS in *Medium*.
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and suitably dilute with *Medium*.
  Chromatographic system
  (See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC
Detector: UV 235 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.2 mL/min
Injection volume: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for the quinine peak
Relative standard deviation: NMT 2.0% for the sum of quinine and dihydroquinine peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ dissolved.

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times D \times V \times 100$$

r_U = sum of the peak responses of quinine and dihydroquinine from the *Sample solution*
r_S = sum of the peak responses of quinine and dihydroquinine from the *Standard solution*
C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
M_{r1} = molecular weight of quinine sulfate, 782.94
M_{r2} = molecular weight of anhydrous quinine sulfate, 746.92
D = dilution factor of the *Sample solution*
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ is dissolved.● (RB 1-Feb-2017)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩
Procedure for content uniformity
Diluent: Hydrochloric acid (1 in 100)
Standard solution: 40 µg/mL of USP Quinine Sulfate RS in *Diluent*
Sample solution: Transfer the contents of one Capsule to a 250-mL volumetric flask, add 175 mL of *Diluent*, and shake by mechanical means for 30 min. Add *Diluent* to volume. Filter a portion of the mixture, discarding the first 20 mL of the filtrate.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Cell: 1 cm
Analytical wavelength: Maximum at about 345 nm
Blank: Water
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$, in the Capsule taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
Standard stock solution: 6 mg/mL of USP Quinine Sulfate RS in diluted alcohol
Standard solution A: 0.06 mg/mL of USP Quinine Sulfate RS from the *Standard stock solution* in diluted alcohol
Standard solution B: 0.05 mg/mL of USP Quininone RS (corresponding to 0.06 mg/mL of the sulfate) and 0.10 mg/mL of cinchonidine (corresponding to 0.12 mg/mL of the sulfate) in diluted alcohol
Sample solution: Nominally 6 mg/mL of quinine sulfate in diluted alcohol prepared as follows. Shake the equivalent of 150 mg of quinine sulfate from the contents of Capsules with 25 mL of diluted alcohol for 10 min, and filter.
Chromatographic system
(See *Chromatography* ⟨621⟩, *General Procedures, Thin-Layer Chromatography*.)
Mode: TLC
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Application volume: 10 µL
Developing solvent system: Chloroform, acetone, and diethylamine (50:40:10). [NOTE—The solvent chamber being used without previous equilibration.]
Analysis
Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*
Proceed as directed in *Chromatography* ⟨621⟩, *General Procedures, Thin-Layer Chromatography*. Allow the spots to dry, and develop the chromatogram using a solvent chamber without previous equilibration. When the solvent front has moved about 15 cm, remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by spraying with glacial acetic acid, and examine under long-wavelength UV light.
Acceptance criteria: Any spot produced by the *Sample solution* at the R_F value of a spot produced by *Standard solution B* is not greater in size or intensity than that corresponding spot. Apart from these spots and from the spot appearing at the R_F value of quinine sulfate, any additional fluorescent spot is not greater in size or intensity than the spot from *Standard solution A*. Spray the plate with potassium iodoplatinate TS. Any spot produced by the *Sample solution* is not greater in size or intensity than a corresponding spot from *Standard solution B*.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

Add the following:

•• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.● (RB 1-Feb-2017)

• **USP REFERENCE STANDARDS** ⟨11⟩
USP Quinine Sulfate RS
USP Quininone RS
Cinchonan-9-one, 6′-methoxy-, (8α)-.
$C_{20}H_{22}N_2O_2$ 322.40