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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.

Delete the following:

▲• **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*.▲ (USP 1-May-2021)

Change to read:

• ▲**B.**▲ (USP 1-May-2021) **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.

Change to read:

• ▲**C.**▲ (USP 1-May-2021) The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **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; ▲10-µm▲ (USP 1-May-2021) 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:

$$\text{Result} = [(r_{b,U} + r_{d,U})/(r_{b,S} + r_{d,S})] \times (C_S/C_U) \blacktriangle\times (M_{r1}/M_{r2})\blacktriangle_{\text{(USP 1-May-2021)}} \times 100$$

$r_{b,U}$ = peak response of quinine from the *Sample solution*

$r_{d,U}$ = peak response of dihydroquinine from the *Sample solution*

$r_{b,S}$ = peak response of quinine from the *Standard solution*

$r_{d,S}$ = peak 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)

$\blacktriangle M_{r1}$ = molecular weight of quinine sulfate, 782.94

M_{r2} = molecular weight of anhydrous quinine sulfate, 746.92 ▲(USP 1-May-2021)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Detector: 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:

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

r_U = absorbance of the *Sample solution*

r_S = absorbance of 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*, as needed

V = volume of *Medium*, 900 mL▲ (USP 1-May-2021)

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 the 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 for 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.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: 0.0144 mg/mL of USP Quinine Sulfate RS in *Medium*

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*

Instrumental conditions

Mode: UV

Analytical wavelength: 248 nm

Cell: 1 cm

Blank: *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:

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

r_U = absorbance of the *Sample solution*

r_S = absorbance of 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,* if necessary

V = volume of *Medium*, 900 mL

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.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

▲▲ (USP 1-May-2021)

IMPURITIES

Delete the following:

▲• **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*.▲ (USP 1-May-2021)

Add the following:

▲• **Organic Impurities, Procedure 1**

Perform both *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.

[Note—The *Standard solution*, *Sample solution*, and *Sensitivity solution* are stable for up to 24 h at 10°.]

Mobile phase: 14.25 g of anhydrous potassium phosphate, monobasic in 1800 mL of water, and add 8 mL of hexylamine. Adjust with diluted phosphoric acid to a pH of 2.3 ± 0.01. Add 30 mL of acetonitrile and dilute with water to 2000 mL.

Diluent: *Mobile phase*

Standard solution: 0.02 mg/mL of USP Quinine Sulfate RS in *Diluent*. Sonicate in cold water to dissolve completely.

Sensitivity solution: 0.002 mg/mL of USP Quinine Sulfate RS from the *Standard solution* in *Diluent*

Sample solution: Nominally 2 mg/mL of quinine sulfate dihydrate in *Diluent* prepared as follows. Weigh accurately 20 Capsules and transfer the Capsule contents, equivalent to 200 mg of quinine sulfate, into a 100-mL volumetric flask. Add 70 mL of *Diluent*, and sonicate for about 15 min in cold water with intermittent shaking. Cool to room temperature and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 316 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 25°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 3 times the retention time of quinine

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.5, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of cinchonidine sulfate and any individual unspecified impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each corresponding impurity from the *Sample solution*

r_S = peak response of quinine 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)

M_{r1} = molecular weight of quinine sulfate, 782.94

M_{r2} = molecular weight of anhydrous quinine sulfate, 746.92

F = relative response factor for each impurity (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.10%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Cinchonidine sulfate[a]	0.43	2.5	2.0
Dihydrocinchonidine sulfate[b,c]	0.64	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Quinidine sulfate[d,c]	0.79	—	—
Quinine sulfate	1.0	1.0	—
Dihydroquinidine sulfate[e,c]	1.29	—	—
Dihydroquinine sulfate[f,g]	1.68	—	—
Any individual unspecified impurity	—	1.0	0.2
Total impurities[h]	—	—	2.5▲ (USP 1-May-2021)

[a] *R*-Quinolin-4-yl[(2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl]methanol sulfate.

[b] (*R*)-[(2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl](quinolin-4-yl)methanol sulfate.

[c] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.

[d] *S*-(6-Methoxyquinolin-4-yl)[(2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl]methanol sulfate dihydrate.

[e] *S*-[(1*S*,2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl](6-methoxyquinolin-4-yl)methanol sulfate.

[f] *R*-[(2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl](6-methoxyquinolin-4-yl)methanol sulfate.

[g] Dihydroquinine sulfate is part of the drug substance and not to be included in the total impurities.

[h] Includes quinicine sulfate and quininone sulfate from *Organic Impurities, Procedure 2*.

Add the following:

▲• **Organic Impurities, Procedure 2**

Organic Impurities, Procedure 2 is applicable only for the impurities quinicine sulfate and quininone sulfate.

[Note—The *Standard solution* and *Sample solution* are stable for up to 25 h at 10°.]

Buffer: 2.72 g/L of anhydrous potassium dihydrogen orthophosphate in water. Add 2 mL of triethylamine and adjust with dilute orthophosphoric acid to a pH of 7.0 ± 0.01.

Solution A: Acetonitrile, methanol, and *Buffer* (23:10:67)

Solution B: Acetonitrile and *Buffer* (70:30)

Diluent: *Solution A*

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
20	100	0
40	40	60
45	100	0
50	100	0

Standard stock solution: 0.5 mg/mL of USP Quinine Sulfate RS in *Diluent*. Sonicate in cold water to dissolve completely.

Standard solution: 0.01 mg/mL of USP Quinine Sulfate RS in *Diluent* from *Standard stock solution*

Sample solution: Nominally 1 mg/mL of quinine sulfate dihydrate in *Diluent* prepared as follows. Weigh accurately 20 Capsules and transfer the Capsule contents, equivalent to 100 mg of quinine sulfate, into a 100-mL volumetric flask. Add 70% of the final volume of *Diluent*, and sonicate for about 15 min in cold water with intermittent shaking. Cool to room temperature and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Temperatures

Autosampler: 10°

Column: 50°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of quinine 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)

M_{r1} = molecular weight of quinine sulfate, 782.94

M_{r2} = molecular weight of anhydrous quinine sulfate, 746.92

F = relative response factor for each impurity (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Quinicine sulfate[a]	0.45	0.63	0.15
Quinine sulfate	1.0	1.0	—
Quininone sulfate[b]	2.54	0.77	1.0▲ (USP 1-May-2021)

[a] 1-(6-Methoxyquinolin-4-yl)-3-[(3*R*,4*R*)-3-vinylpiperidin-4-yl]propan-1-one sulfate.

[b] (6-Methoxyquinolin-4-yl)[(2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl]methanone sulfate.

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in tight containers. ▲Store at controlled room temperature.▲ (USP 1-May-2021)

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Quinine Sulfate RS

▲▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
QUININE SULFATE CAPSULES	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

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