Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 4, and 12 hours.

Procedure—Using filtered portions of the solution under test, diluted with 0.1 N hydrochloric acid if necessary, determine the amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 248 nm by comparison with a Standard solution having a known concentration of USP Quinidine Sulfate RS in the same *Medium*.

Tolerances—The percentages of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 50%
4	between 43% and 73%
12	not less than 70%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 4, and 12 hours.

Procedure—Proceed as directed for *Test 1*.

Tolerances—The percentages of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 10% and 35%
4	between 30% and 55%
12	not less than 75%

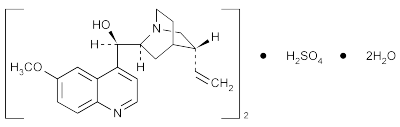
Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Procedure for content uniformity—Proceed as directed for *Procedure for content uniformity* in the test for *Uniformity of dosage units* under *Quinidine Sulfate Capsules,* using 1 powdered Tablet instead of the contents of 1 Capsule.

Chromatographic purity—Shake a quantity of powdered Tablets, equivalent to about 150 mg of quinidine sulfate, with 25 mL of diluted alcohol for 10 minutes, and filter. Using the filtrate as the *Test preparation,* proceed as directed in the test for *Chromatographic purity* under *Quinidine Sulfate*.

Assay—Proceed as directed in the *Assay* under *Quinidine Sulfate Capsules,* using powdered Tablets.

Quinine Sulfate



$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ 782.94

Cinchonan-9-ol, 6′-methoxy-, (8α,9*R*)-, sulfate (2:1) (salt), dihydrate.

Quinine sulfate (2:1) (salt) dihydrate [6119-70-6].

Anhydrous 746.93 [804-63-7].

» Quinine Sulfate is the sulfate of an alkaloid obtained from the bark of species of *Cinchona.* It contains not less than 99.0 percent and not more than 101.0 percent of total alkaloid salt, calculated as $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$, on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩**—**
USP Quinine Sulfate RS
USP Quininone RS
$C_{20}H_{22}N_2O_2$ 322.40

Identification—

A: A 1 in 2000 solution in dilute sulfuric acid (1 in 350) exhibits a vivid blue fluorescence. On the addition of a few drops of hydrochloric acid, the fluorescence disappears.

B: In the test for *Chromatographic purity*, the R_F value of the principal spot obtained from the *Test preparation* corresponds to that from the *Standard preparation*.

C: A solution (1 in 50) made with the aid of a few drops of hydrochloric acid responds to the tests for *Sulfate* ⟨191⟩.

Specific rotation ⟨781S⟩: between –235° and –245°.

Test solution: 20 mg per mL, in 0.1 N hydrochloric acid.

Water, *Method I* ⟨921⟩: between 4.0% and 5.5%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Chloroform-alcohol-insoluble substances—Warm 2 g with 15 mL of a mixture of chloroform and dehydrated alcohol (2:1) at about 50° for 10 minutes. Filter through a tared, sintered-glass filter, using gentle suction. Wash the filter with five 10-mL portions of the chloroform-alcohol mixture, dry at 105° for 1 hour, and weigh: the weight of the residue does not exceed 2 mg (0.1%).

Chromatographic purity—

Standard preparation—Prepare a solution of USP Quinine Sulfate RS in diluted alcohol to contain 6 mg per mL.

Diluted standard preparation—Dilute a portion of the *Standard preparation* with diluted alcohol to a concentration of 0.06 mg per mL.

Related substances preparation—Prepare a solution in diluted alcohol containing in each mL 0.05 mg each of USP Quininone RS (corresponding to 0.06 mg of the sulfate), and 0.10 mg of cinchonidine (corresponding to 0.12 mg of the sulfate).

Test preparation—Prepare a solution of Quinine Sulfate in diluted alcohol to contain 6 mg per mL.

Procedure—Apply 10-µL portions of the *Test preparation*, the *Standard preparation*, the *Diluted standard preparation*, and the *Related substances preparation* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Allow to dry, and develop the chromatogram in a solvent system consisting of a mixture of chloroform, acetone, and diethylamine (5:4:1), the solvent chamber being used 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. Spray the chromatogram with glacial acetic acid. Locate the spots on the plate by examination under long-wavelength UV light. Any spot produced by the *Test preparation* at the R_F value of a spot produced by the *Related substances preparation* 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 of the *Diluted standard preparation.* Spray the plate with potassium iodoplatinate TS. Any spot produced by the *Test preparation* is not greater in size or intensity than a corresponding spot from the *Related substances preparation*.

Limit of dihydroquinine sulfate—

Methanesulfonic acid solution—Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, dilute with water to 500 mL, and mix.

Diethylamine solution—Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.

Mobile phase—Prepare a suitable filtered and degassed mixture of water, acetonitrile, *Methanesulfonic acid solution*, and *Diethylamine solution* (860:100:20:20). Adjust with *Diethylamine solution* to a pH of 2.6 if found to be lower.

System suitability preparation—Transfer about 10 mg each of quinine sulfate and dihydroquinine to a 50-mL volumetric flask. Dissolve in about 5 mL of methanol, dilute with *Mobile phase* to volume, and mix.

System suitability test—Chromatograph injections of the *System suitability preparation* as directed for *Procedure:* the relative retention times for quinine and dihydroquinine are about 1 and 1.5, respectively. The resolution between the quinine and dihydroquinine peaks is not less than 1.2. The relative standard deviation for the peak response of quinine is not more than 2.0%.

Test preparation—Transfer about 20 mg of Quinine Sulfate to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure (see *Chromatography* ⟨621⟩)—Inject about 50 µL of the *Test preparation* into a chromatograph equipped with a 235-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The response of the dihydroquinine peak is not greater than one-ninth that of the quinine peak (10.0%).

Assay—Dissolve about 200 mg of Quinine Sulfate, accurately weighed, in 20 mL of acetic anhydride, add 4 drops of *p*-naphtholbenzein TS, and titrate with 0.1 N perchloric acid VS from a 10-mL microburet to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 24.90 mg of total alkaloid salt, calculated as $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$.

Quinine Sulfate Capsules

» Quinine Sulfate Capsules contain amounts of quinine sulfate and dihydroquinine sulfate totaling not less than 90.0 percent and not more than 110.0 percent of the labeled amount of quinine sulfate, calculated as $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Quinine Sulfate RS
USP Quininone RS
$C_{20}H_{22}N_2O_2$ 322.40

Identification—

A: Shake well a quantity of the contents of Capsules, equivalent to about 100 mg of quinine sulfate, with 100 mL of dilute sulfuric acid (1 in 350), and filter. 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: In the test for *Chromatographic purity*, the R_F value of the principal spot obtained from the *Test preparation* corresponds to that from the *Standard preparation.*

C: Shake a quantity of the contents of Capsules, equivalent to about 20 mg of quinine sulfate, with 10 mL of dilute hydrochloric acid (1 in 100), and filter: the filtrate responds to the tests for *Sulfate* ⟨191⟩.

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

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 248 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, in comparison with a Standard solution having a known concentration of USP Quinine Sulfate RS in the same *Medium*.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ is dissolved in 45 minutes.

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

Procedure for content uniformity—Transfer the contents of 1 Capsule to a 250-mL volumetric flask, add about 175 mL of dilute hydrochloric acid (1 in 100), and shake by mechanical means for 30 minutes. Add dilute hydrochloric acid (1 in 100) to volume, and mix. Filter a portion of the mixture, discarding the first 20 mL of the filtrate. Concomitantly determine the absorbances of this solution, quantitatively diluted, if necessary, and a Standard solution of USP Quinine Sulfate RS in dilute hydrochloric acid (1 in 100) having a known concentration of about 40 µg per mL, in 1-cm cells, at the wavelength of maximum absorbance at about 345 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of active ingredients, calculated as quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$, in the Capsule taken by the formula:

$$(TC / D)(A_U / A_S)$$

in which T is the labeled quantity, in mg, of quinine sulfate in the Capsule, D is the concentration, in µg per mL, of quinine sulfate in the solution from the Capsule, based on the labeled quantity per Capsule and the extent of dilution, C is the concentration, in µg per mL, of USP Quinine Sulfate in the Standard solution, and A_U and A_S are the absorbances of the solution from the Capsule and the Standard solution, respectively.

Chromatographic purity—Shake a quantity of the contents of Capsules, equivalent to about 150 mg of quinine sulfate, with 25 mL of diluted alcohol for 10 minutes, and filter. Using this as the test solution, proceed as directed in the test for *Chromatographic purity* under *Quinine Sulfate*.

Assay—

Methanesulfonic acid solution, *Diethylamine solution*, *Mobile phase*, *System suitability preparation*, and *System suitability test*—Proceed as directed in the test for *Limit of dihydroquinine sulfate* under *Quinine Sulfate*.

Standard preparation—Transfer about 20 mg of USP Quinine Sulfate RS, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer the contents of not less than 20 Capsules to a container, and mix. Transfer an accurately weighed portion of the powder, equivalent to about 160 mg of quinine sulfate, to a 100-mL volumetric flask, add 80 mL of methanol, and shake the flask by mechanical means for 30 minutes. Dilute with methanol to volume, and filter, discarding the first 10 mL of the filtrate. Transfer 3.0 mL of the filtrate to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure (see *Chromatography* ⟨621⟩)—Inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into a chromatograph equipped with a 235-nm detector and a 3.9-mm × 30-cm column that contains packing L1. Calculate the quantity, in mg, of the sum of quinine sulfate and