Hydroxychloroquine Sulfate Tablets

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Expert Committee	Small Molecules 1

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 1 Expert Committee has revised the Hydroxychloroquine Sulfate Tablets monograph. The purpose of this revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*.

The Hydroxychloroquine Sulfate Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).

Revision Bulletin
Official: June 1, 2022

Hydroxychloroquine Sulfate Tablets

DEFINITION

Hydroxychloroquine Sulfate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$).

IDENTIFICATION

● **A. Identification—Organic Nitrogenous Bases ⟨181⟩**

Sample solution: Nominally 20 mg/mL of hydroxychloroquine sulfate in water prepared as follows. Triturate a quantity of finely powdered Tablets, equivalent to about 1 g of hydroxychloroquine sulfate, with 50 mL of water, and filter (retain the remainder of the filtrate for *Identification B*).

Acceptance criteria: The clear filtrate meets the requirements.

● **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sulfate*:** The clear filtrate obtained from *Identification A* meets the requirements.

● **C.** 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: Acetonitrile, water, and phosphoric acid (100:900:2)

Solution B: Acetonitrile, water, and phosphoric acid (800:200:1)

Mobile phase: *Solution A* and *Solution B* (97:3)

Standard solution: 0.01 mg/mL of USP Hydroxychloroquine Sulfate RS in *Solution A* prepared as follows. Transfer a suitable quantity of USP Hydroxychloroquine Sulfate RS to a suitable volumetric flask, and add *Solution A* to about 75% of the flask volume. Sonicate for NLT 5 min or until solids are dissolved. Dilute with *Solution A* to volume.

Sample stock solution: Nominally 1.0 mg/mL of hydroxychloroquine sulfate in *Solution A* prepared as follows. Transfer a portion of finely ground powder, from NLT 20 Tablets, equivalent to about 200 mg of hydroxychloroquine sulfate to a 200-mL volumetric flask and add *Solution A* to about 75% of the flask volume. Sonicate for NLT 10 min or until solids are dissolved. Dilute with *Solution A* to volume.

Sample solution: Nominally 0.01 mg/mL of hydroxychloroquine sulfate in *Solution A* from *Sample stock solution*. Pass through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 2.0-mm × 10-cm; 2-µm packing L1

Column temperature: 35°

Flow rate: 0.8 mL/min

Injection volume: 3 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of hydroxychloroquine from the *Sample solution*

r_S = peak response of hydroxychloroquine from the *Standard solution*

C_S = concentration of USP Hydroxychloroquine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of hydroxychloroquine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲Test 1▲ (RB 1-Jun-2022)

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 60 min

Standard solution: USP Hydroxychloroquine Sulfate RS in *Medium*

Sample solution: Pass a portion of the solution through a suitable filter. Dilute with *Medium*, if necessary.

Instrumental conditions

Mode: UV

Analytical wavelength: 343 nm

Analysis: Determine the percentage of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$) dissolved.

Tolerances: NLT 70% (*Q*) of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$) is dissolved.

▲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; 500 mL, deaerated

Apparatus 1: 100 rpm

Time: 30 min

Standard solution: 0.013 mg/mL USP Hydroxychloroquine Sulfate RS in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size and discard NLT 5 mL of filtrate. Dilute with *Medium* to a concentration similar to the *Standard solution*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 343 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Hydroxychloroquine Sulfate RS in the *Standard solution* (mg/mL)

D = dilution factor of the *Sample solution*

V = volume of the *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$) is dissolved. ▲ (RB 1-Jun-2022)

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

IMPURITIES

- **Organic Impurities**

Solution A: Acetonitrile, water, and phosphoric acid (100:900:2)

Solution B: Acetonitrile, water, and phosphoric acid (800:200:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	97	3
1.8	97	3
2.5	5	95
3.5	5	95
4.0	97	3
6.0	97	3

Standard stock solution: Use the *Standard solution* from the *Assay*.

Standard solution: 0.001 mg/mL of USP Hydroxychloroquine Sulfate RS in *Solution A* from *Standard stock solution*

Sample stock solution: Nominally 1.0 mg/mL of hydroxychloroquine sulfate in *Solution A* prepared as follows. Transfer a portion of finely ground powder, from NLT 20 Tablets, equivalent to about 200 mg of hydroxychloroquine sulfate, to a 200-mL volumetric flask and add *Solution A* to about 75% of the flask volume. Sonicate for NLT 10 min or until solids are dissolved. Dilute with *Solution A* to volume.

Sample solution: Nominally 0.1 mg/mL of hydroxychloroquine sulfate in *Solution A* from *Sample stock solution*. Pass through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 2.0-mm × 10-cm; 2-µm packing L1

Column temperature: 35°

Flow rate: 0.8 mL/min

Injection volume: 2 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Tablets taken:

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

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

r_S = peak response of hydroxychloroquine from the *Standard solution*

C_S = concentration of USP Hydroxychloroquine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of hydroxychloroquine sulfate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desethyl hydroxychloroquine[a,b]	0.87	1.3	0.5
Hydroxychloroquine	1.0	—	—
Hydroxychloroquine acetate[b,c]	1.52	0.81	—
Sulfohydroxychloroquine[b,d]	2.32	1.0	—
Chloroquine related compound A[b,e]	4.46	2.4	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	2.0

[a] 2-({4-[(7-Chloroquinolin-4-yl)amino]pentyl}amino)ethan-1-ol.
[b] Process impurity monitored in the drug substance monograph.
[c] 2-({4-[(7-Chloroquinolin-4-yl)amino]pentyl}ethylamino)ethyl acetate.
[d] 2-({4-[(7-Chloroquinolin-4-yl)amino]pentyl}ethylamino)ethyl hydrogen sulfate.
[e] 4,7-Dichloroquinoline.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.

Add the following:

▲- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Jun-2022)

- **USP Reference Standards** ⟨11⟩

  USP Hydroxychloroquine Sulfate RS

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