Quinidine Gluconate Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	7-Oct-2021
Official Date	8-Oct-2021
Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Quinidine Gluconate Extended-Release Tablets monograph. The purpose of this revision is to add *Dissolution Test 6* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). Existing references to reagents have been updated for consistency with the reagent entry. Footnote 1 under *Dissolution Test 5* has been updated to the current weblink of the suitable sinker.

The Quinidine Gluconate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Robyn Fales, Scientist IV (240-221-2047 or rnp@usp.org).

Revision Bulletin
Official: October 8, 2021

Quinidine Gluconate Extended-Release Tablets

DEFINITION

Quinidine Gluconate Extended-Release Tablets contain amounts of quinidine gluconate and dihydroquinidine gluconate totaling NLT 90.0% and NMT 110.0% of the labeled amount of quinidine gluconate, calculated as quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$).

IDENTIFICATION

● **A.**

Sample solution: Shake an amount, equivalent to 50 mg of quinidine gluconate from powdered Tablets, with 100 mL of dilute sulfuric acid (1 in 350), and filter.

Acceptance criteria: The filtrate so obtained exhibits a vivid blue fluorescence when viewed under long-wavelength UV light. On the addition of hydrochloric acid, the fluorescence disappears.

● **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **C.** The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in *Organic Impurities*.

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 prepare a 100-mL 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 found to be lower.

System suitability solution: Transfer 10 mg each of quinidine gluconate and dihydroquinidine hydrochloride to a 50-mL volumetric flask. Dissolve in 5 mL of methanol, and dilute with *Mobile phase* to volume.

Standard solution: 0.2 mg/mL of USP Quinidine Gluconate RS in *Mobile phase*

Sample stock solution: To an amount equivalent to 160 mg of quinidine gluconate from NLT 20 finely powdered Tablets in a 100-mL volumetric flask add 80 mL of a mixture of methanol and water (1:1), and sonicate until evenly dispersed. Cool to room temperature, dilute with a mixture of methanol and water (1:1) to volume, and filter, discarding the first 20 mL of the filtrate.

Sample solution: 0.19 mg/mL of quinidine gluconate in *Mobile phase* prepared as follows. Transfer 3.0 mL of the *Sample stock solution* to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 235 nm

Column: 3- to 5-mm × 25- to 30-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—The relative retention times for quinidine and dihydroquinidine are 1 and 1.5, respectively, for the *System suitability solution*.]

Suitability requirements

Resolution: NLT 1.2 between quinidine and dihydroquinidine, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the sum of the percentages of quinidine gluconate and dihydroquinidine gluconate in the Tablets 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 response of quinidine from the *Sample solution*

$r_{D,U}$ = peak response of dihydroquinidine from the *Sample solution*

$r_{B,S}$ = peak response of quinidine from the *Standard solution*

$r_{D,S}$ = peak response of dihydroquinidine from the *Standard solution*

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

C_U = nominal concentration of quinidine gluconate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

● **Dissolution** ⟨711⟩

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: Add 6.9 g of anhydrous sodium acetate and 0.525 mL of glacial acetic acid to 1 L of water. Adjust with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of 5.4; 900 mL.

Apparatus 2: 75 rpm

Times: 1, 2, 4, and 8 h

Standard solution: A known concentration of USP Quinidine Gluconate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium* if necessary, in comparison with the *Standard solution* concentration.

Instrumental conditions

Mode: UV

Analytical wavelength: 235 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved from UV absorbances of the *Sample solution* and *Standard solution*.

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved
1	30%–50%
2	45%–65%
4	60%–85%
8	NLT 85%

The percentages of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: 0.1 N hydrochloric acid; 600 mL

Apparatus 2: 75 rpm

Times: Proceed as directed for *Test 1*.

Standard solution: A known concentration of USP Quinidine Gluconate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium* if necessary, in comparison with the *Standard solution* concentration.

Instrumental conditions

Mode: UV

Analytical wavelength: 235 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved from UV absorbances of the *Sample solution* and *Standard solution*.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved
1	30%–45%
2	45%–60%
4	60%–80%
8	NLT 85%

The percentages of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: Proceed as directed for *Test 1*.

Apparatus: Proceed as directed for *Test 1*, using 8-mesh sinker baskets.[1]

Times: 1, 2, and 4 h

Standard solution: USP Quinidine Gluconate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary, in comparison with the *Standard solution* concentration.

Instrumental conditions

Mode: UV

Analytical wavelength: 235 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved from the UV absorbances of the *Sample solution* and the *Standard solution.*

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved
1	20%–50%
2	40%–70%
4	NLT 75%

The percentages of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩*, Acceptance Table 2*.

▲**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: pH 5.4 acetate buffer prepared as follows. Add 6.9 g of anhydrous sodium acetate and 0.53 mL of glacial acetic acid to 1 L of water. Adjust with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of 5.4; 900 mL, deaerated.

Apparatus 2: 75 rpm, using 8-mesh sinker baskets[1]

Times: 1, 2, 3, and 5 h

Standard solution: 0.012 mg/mL of USP Quinidine Gluconate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

(See Ultraviolet-Visible Spectroscopy ⟨857⟩.)

Mode: UV

Analytical wavelength: 235 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) in the sample withdrawn at each time point (i):

$$\text{Result}_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of quinidine gluconate in the portion of sample withdrawn at time point (i) (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at time point (*i*) (mL)

Tolerances: See *Table 4*.

Table 4

Time point (*i*)	Time (h)	Amount Dissolved (%)
1	1	17–37
2	2	37–57
3	3	60–80
4	5	NLT 80

The percentages of the labeled amount of quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*. ▲ (RB 8-Oct-2021)

- **Uniformity of Dosage Units** ⟨905⟩

Procedure for content uniformity

Standard solution: 0.0525 mg/mL of USP Quinidine Gluconate RS in 0.1 N hydrochloric acid

Sample solution: Transfer 1 intact or powdered Tablet to a 250-mL volumetric flask, and add 125 mL of 0.1 N hydrochloric acid. Heat the sample with frequent agitation just to boiling, and cool to room temperature. Dilute with 0.1 N hydrochloric acid to volume, mix, and filter, discarding the first 20 mL of filtrate. If necessary, further dilute quantitatively with 0.1 N hydrochloric acid.

Instrumental conditions

Mode: UV

Cell: 1 cm

Analytical wavelength: 347 nm

Blank: 0.1 N hydrochloric acid

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Concomitantly determine the absorbances of the *Samples*.

Calculate the percentage of the labeled amounts of active ingredients, calculated as quinidine gluconate ($C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$), in the Tablet 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 Quinidine Gluconate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinidine gluconate in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements

IMPURITIES

- **Organic Impurities**

Standard solution A: 6 mg/mL of USP Quinidine Gluconate RS in diluted alcohol

Standard solution B: 0.06 mg/mL of USP Quinidine Gluconate RS in diluted alcohol from *Standard solution A*

Standard solution C: 0.04 mg/mL of USP Quininone RS (corresponding to 0.06 mg of the gluconate) in diluted alcohol

Sample solution: Nominally equivalent to 6 mg/mL of quinidine gluconate prepared as follows. Shake a quantity of powdered Tablets, equivalent to about 150 mg of quinidine gluconate, 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)

Analysis

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Sample solution*

Proceed as directed in the chapter. The solvent chamber is used without previous equilibration. When the solvent front has moved 15 cm, remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Spray with glacial acetic acid. Locate the spots on the plate by examination 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 C* is not greater in size or intensity than that corresponding spot. Apart from these spots and from the spots appearing at the R_F value of quinidine gluconate and dihydroquinidine gluconate (the two spots most evident from *Standard solution A*), any additional fluorescent spot is not greater in size or intensity than the principal spot of *Standard solution B*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed, light-resistant containers.
- **Labeling:** The labeling indicates the *Dissolution Test* with which the product complies.
- **USP Reference Standards** ⟨11⟩

USP Quinidine Gluconate RS

USP Quininone RS

Cinchonan-9-one, 6′-methoxy-, (8α)-.

$C_{20}H_{22}N_2O_2$ 322.40

[1] A suitable sinker is available from ▲www.agilent.com,▲ (RB 8-Oct-2021) catalog number 12-3062.

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