

## Quinidine Gluconate Extended-Release Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	26-Feb-2021
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Quinidine Gluconate Extended-Release Tablets monograph.

The purpose for the 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). In addition, existing references to reagents are being updated for consistency with the reagent entry names. For additional information about reagent cross references, please see the related [Compendial Notice](#). The weblink to a suitable sinker in footnote 1 for *Dissolution Test 5* is also being updated.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.<sup>1</sup>

Should you have any questions, please contact Sujatha Ramakrishna, Principal Scientific Liaison (301-816-8349 or [sxr@usp.org](mailto:sxr@usp.org)).

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<sup>1</sup> This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

## 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.<sup>1</sup>

**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<sup>1</sup>

**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

Time point (i)	Time (h)	Amount Dissolved (%)
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](#). ▲ (TBD)

● **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 Quinone 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  $\mu$ L

**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-, (8 $\alpha$ )-.

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

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<sup>1</sup> A suitable sinker is available from [www.agilent.com](http://www.agilent.com), (TBD) catalog number 12-3062.

### Page Information:

Not Applicable

### DocID:

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