Quetiapine Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	27–Oct–2017
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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Quetiapine Extended-Release Tablets monograph. The purpose for the revision is to:

- Add *Dissolution Test* 2, *Test* 3, and *Test* 4 to accommodate drug products which were approved by the FDA with different dissolution conditions and acceptance criteria. Add a *Labeling* section for the new tests.
- Revise the calculations in Dissolution *Test* 1 to reflect that the volume of *Medium* is kept constant throughout the test.
- Revise the definition of C_i in Dissolution *Test* 1.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Quetiapine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement to *USP 41–NF 36*.

Should you have any questions, please contact K. Kalyana Seela, Ph.D., Senior Scientific Liaison (kks@usp.org).

Quetiapine Extended-Release Tablets

DEFINITION

Quetiapine Extended-Release Tablets contain quetiapine fumarate [$(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$] equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$).

IDENTIFICATION

- **A. Infrared Absorption** ⟨197F⟩
  Standard solution: Transfer 10 mg of USP Quetiapine Fumarate RS to a suitable vial. Add 10 mL of acetone and cap the vial. Sonicate for about 10 min. Allow the solution to equilibrate to room temperature. Evaporate the acetone completely. Add 2 mL of chloroform. Gently swirl for several minutes. Pass through a suitable filter of 0.45-µm pore size. Use the filtrate.
  Sample solution: Grind NLT 10 Tablets. Transfer an amount of powder equivalent to NLT 10 mg of quetiapine fumarate to a suitable vial. Add 10 mL of acetone and cap the vial. Sonicate for about 10 min. Allow the solution to equilibrate to room temperature. Evaporate the acetone completely. Add 2 mL of chloroform. Gently swirl for several minutes. Pass through a suitable filter of 0.45-µm pore size. Use the filtrate.
  Acceptance criteria: Meet the requirements
- **B.** 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**
  Buffer: Dissolve 2.6 g/L of dibasic ammonium phosphate in water.
  Mobile phase: Methanol, acetonitrile, and *Buffer* (54:7:39)
  Diluent: Acetonitrile and water (50:50)
  System suitability stock solution: 0.05 mg/mL of USP Quetiapine Related Compound H RS in *Mobile phase*
  System suitability solution: 0.005 mg/mL of USP Quetiapine Related Compound H RS and 0.5 mg/mL of USP Quetiapine System Suitability RS in *Mobile phase* prepared as follows. Transfer 5 mg of USP Quetiapine System Suitability RS to a 10-mL volumetric flask. Add 7 mL of *Mobile phase* and sonicate to dissolve. Transfer 1 mL of *System suitability stock solution* to the volumetric flask. Dilute with *Mobile phase* to volume.
  Standard solution: 0.2 mg/mL of USP Quetiapine Fumarate RS in *Mobile phase*
  Sample stock solution: Transfer NLT 5 Tablets to a homogenizer vessel. Add 50 mL of acetonitrile, swirl to wet, and allow to stand for approximately 10 min. Add an additional 160 mL of *Diluent* and extract for about 10 min. Transfer the contents of the homogenizer to a 500-mL volumetric flask. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate.
  Sample solution: Nominally 0.16–0.18 mg/mL of quetiapine from the *Sample stock solution* in *Mobile phase*
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 230 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L7
  Flow rate: 1.3 mL/min
  Injection volume: 30 µL
  Run time: NLT 2.5 times the retention time of quetiapine
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [Note—See *Table 5* for the relative retention times.]
  Suitability requirements
  Resolution: NLT 1.5 between quetiapine related compound G and quetiapine related compound H; NLT 2.0 between the quetiapine desthoxy and quetiapine peaks; *System suitability solution*
  Tailing factor: NMT 1.5, *Standard solution*
  Relative standard deviation: NMT 2.0%, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Quetiapine Fumarate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of quetiapine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
N = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩
  •**Test 1**• (RB 1-Nov-2017)
  Medium 1: Citrate buffer, pH 4.8. Dissolve 9.6 g of anhydrous citric acid in 600 mL of water. Add 90 mL of 1 N sodium hydroxide. Dilute with water to 1 L; 900 mL.
  Medium 2: Dissolve 17.9 •g• (RB 1-Nov-2017) of dibasic sodium phosphate dodecahydrate in 400 mL of water. Add 460 mL of 1 N sodium hydroxide and dilute with water to 1 L; 100 mL.
  [Note—It is recommended to check the pH of the mixture of 90 mL of *Medium 1* and 10 mL of *Medium 2,* which should be between 6.4 and 6.8. If the pH of the mixture is less than 6.4, 10 mL/L of 1 N sodium hydroxide may be added to *Medium 2*. If the pH of the mixture is greater than 6.8, 10 mL/L of 1 N hydrochloric acid may be added to *Medium 2*.]
  Start the test with 900 mL of *Medium 1*. Add 100 mL of *Medium 2* to the vessel after 5 h of the test and continue the test.
  Apparatus 1: 200 rpm
  Times: 1, 6, 12, and 20 h
  Diluent: *Medium 1* and *Medium 2* (90:10)
  Standard solution: (*L*/400) mg/mL of USP Quetiapine Fumarate RS in *Diluent*, where *L* is the label claim in mg/Tablet
  Sample solution: Pass a suitable portion of the solution under test through a suitable filter.

Instrumental conditions
Mode: UV
Analytical wavelength: About 290 nm
Blank: *Diluent*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration, C_i, of quetiapine ($C_{21}H_{25}N_3O_2S$) in *Medium* (mg/mL) after time point (*i*):

$$C_i = (A_U/A_S) \times C_S \times (M_{r1}/M_{r2}) \times N$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of •quetiapine fumarate in• (RB 1-Nov-2017) the *Standard solution* (mg/mL)
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
N = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at each time point (*i*):

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

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

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

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

C_i• (RB 1-Nov-2017) = concentration of quetiapine in *Medium* in the portion of sample withdrawn at •each time point• (RB 1-Nov-2017) (mg/mL)
V = volume of *Medium*, 900 mL for 1 h; 1000 mL for 6-, 12-, and 20-h time points
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	6	47–69
3	12	65–95
4	20	NLT 85

The percentages of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 2, 4, 8, and 24 h
Standard solution: 0.03 mg/mL of USP Quetiapine Fumarate RS in water
Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of filtrate. Replace the volume withdrawn with an equal volume of *Medium*. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions
Mode: UV
Analytical wavelength: 290 nm
Blank: Water
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration, C_i, of quetiapine ($C_{21}H_{25}N_3O_2S$) in *Medium* (mg/mL) after each time point (*i*):

$$C_i = (A_U/A_S) \times C_S \times D \times (M_{r1}/M_{r2}) \times N$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of quetiapine fumarate in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*, if needed
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
N = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at each time point (*i*):

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

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

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

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

C_i = concentration of quetiapine in *Medium* in the portion of sample withdrawn at each time point (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	5–25
2	4	20–45
3	8	45–75
4	24	NLT 85

The percentages of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Times: 1, 4, and 8 h
Standard solution: USP Quetiapine Fumarate RS, equivalent to (*L*/900) mg/mL of quetiapine in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a suitable portion of the solution under test through a suitable full flow filter of 10-µm pore size.
Instrumental conditions
Mode: UV
Analytical wavelength: 295 nm
Cell
For 50-mg Tablets: 10 mm
For 150-, 200-, 300-, and **400-mg Tablets:** 1 mm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at each time point (*i*):

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times N \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of quetiapine fumarate in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
N = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (for 50-, 150-, and 200-mg Tablets) (%)	Amount Dissolved (for 300- and 400-mg Tablets) (%)
1	1	NMT 40	NMT 35
2	4	55–75	45–65
3	8	NLT 85	NLT 80

The percentages of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) 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: Water; 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, 8, and 16 h
Standard solution: USP Quetiapine Fumarate RS, equivalent to (*L*/900) mg/mL of quetiapine in *Medium*, where *L* is the label claim in mg/Tablet
Sample solution: Pass a suitable portion of the solution under test through a suitable filter.
Instrumental conditions
Mode: UV
Analytical wavelength: 250 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at each time point (*i*):

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times N \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of quetiapine fumarate in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
N = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Tolerances: See *Table 4*. The percentages of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*. ● (RB 1-Nov-2017)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Buffer, Mobile phase, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability
Sample: *System suitability solution*
[NOTE—See *Table 5* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between quetiapine related compound G and quetiapine related compound H; NLT 2.0 between the quetiapine desthoxy and quetiapine peaks
Analysis
Sample: *Sample solution*
[NOTE—See *Table 5* for the relative retention times.]
Calculate the percentage of each degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product from the *Sample solution*
r_S = peak response of quetiapine from the *Sample solution*
F = relative response factor for the corresponding degradation product from *Table 5*

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (for 50-mg Tablets) (%)	Amount Dissolved (for 150-mg Tablets) (%)	Amount Dissolved (for 200-mg Tablets) (%)	Amount Dissolved (for 300-mg Tablets) (%)	Amount Dissolved (for 400-mg Tablets) (%)
1	1	NMT 20	NMT 20	NMT 20	NMT 15	NMT 15
2	4	30–55	35–55	28–48	22–42	22–42
3	8	60–85	65–90	60–85	52–76	50–75
4	16	NLT 85	NLT 85	NLT 85	NLT 85	NLT 85

Acceptance criteria: See *Table 5*. Disregard peaks less than 0.05%.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fumaric acid[a]	0.1	—	—
Quetiapine related compound G	0.48	1.4	0.2
Quetiapine related compound H	0.57	1.0	0.2
Quetiapine desethoxy[b]	0.87	—	—
Quetiapine	1.0	—	—
Quetiapine related compound B[b]	1.9	—	—
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	0.4

[a] Counter ion peak, not to be included in the total impurities.

[b] Process impurity controlled in the drug substance. Included for identification purposes only. Not reported for the drug product and not included in the total impurities.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. (RB 1-Nov-2017)
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Quetiapine Fumarate RS
  USP Quetiapine Related Compound H RS
  4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)-1-[2-(2-hydroxyethoxy)ethyl]piperazine 1-oxide.
  $C_{21}H_{25}N_3O_3S$ 399.51
  USP Quetiapine System Suitability RS
  It contains quetiapine fumarate and at least 0.1% of each of the following impurities:
  Quetiapine related compound B: 11-(Piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine; Quetiapine related compound G: Dibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one; and Quetiapine desethoxy: 2-[4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.