Quetiapine Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
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Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Quetiapine Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 8* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 8* was validated using a Zorbax SB C8 brand of L7 column. The typical retention time for quetiapine is about 0.8 min.

Additionally, the table number within the test for *Organic Impurities* and references to this table number were 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.[1]

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

[1] 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*.

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. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 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

Change to read:

- **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 9*▲ (TBD) 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

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 of dibasic sodium phosphate dodecahydrate in 400 mL of water. Add 460 mL of 1 N sodium hydroxide VS 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 VS 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 VS 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 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*):

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

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

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

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

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 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 VS; 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*.

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

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

Medium, Apparatus 1, Times, Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Dissolution Test 2*.

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	10–30
2	4	30–50
3	8	60–80
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 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: pH 6.8 phosphate buffer (6.8 g/L of monobasic potassium phosphate and 0.9 g/L of sodium hydroxide in water. Adjust with 1 N sodium hydroxide VS or phosphoric acid to a pH of 6.8, and sonicate for NLT 10 min); 900 mL

Apparatus 2: 100 rpm, with sinker

Times: 1, 4, 8, and 16 h

Mobile phase: Methanol, trifluoroacetic acid, and water (40:0.1:60)

Standard solution: 0.1 mg/mL of USP Quetiapine Fumarate RS prepared as follows. Transfer an appropriate amount of USP Quetiapine Fumarate RS to a suitable volumetric flask, and add 5% of the final flask volume of methanol. Sonicate to dissolve, then dilute with *Medium* to volume.

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.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm
Column: 4.6-mm × 5.0-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
Run time: NLT 2.0 times the retention time of quetiapine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

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*):

$$C_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times N$$

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)

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*):

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

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

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

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

C_i = concentration of 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 *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (for 50- and 150-mg Tablets) (%)	Amount Dissolved (for 200-, 300-, and 400-mg Tablets) (%)
1	1	NMT 15	NMT 10
2	4	21–41	21–41
3	8	56–76	51–71
4	16	NLT 80	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 7: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Acid stage medium: Citrate buffer, pH 4.8 (9.6 g/L of anhydrous citric acid in water prepared as follows. Transfer a suitable quantity of anhydrous citric acid to an appropriate volumetric flask. Dissolve in 60% of the flask volume of water, then add 9% of the flask volume of 1 N sodium hydroxide VS. Dilute with water to volume); 900 mL, deaerated

0.05 M phosphate buffer solution: 17.9 g/L of dibasic sodium phosphate dodecahydrate solution prepared as follows. Transfer a suitable amount of dibasic sodium phosphate dodecahydrate to an appropriate volumetric flask containing 40% of the flask volume of water. Add 46% of the flask volume of 1 N sodium hydroxide VS and dilute with water to volume.

Buffer stage medium: Phosphate buffer, pH 6.6 (add 100 mL of *0.05 M phosphate buffer solution* to the *Acid stage medium*; adjust with 1 N sodium hydroxide VS or 1 N hydrochloric acid VS to obtain a pH of 6.6 ± 0.20, if necessary); 1000 mL

Apparatus 1: 20-mesh basket; 200 rpm

Times: 1 and 4 h in *Acid stage medium*; 6, 10, and 16 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

Procedure: Run the test in the *Acid stage medium* for the times specified. After 5 h, add 100 mL of *0.05 M phosphate buffer solution* and continue running the test in *Buffer stage medium* for the times specified.

Standard stock solution: 1.2 mg/mL of USP Quetiapine Fumarate RS prepared as follows. Transfer an appropriate amount of USP Quetiapine Fumarate RS into a suitable volumetric flask. Add 40% of the flask volume of methanol and sonicate to dissolve. Dilute with water to volume.

Acid stage standard solution: 0.03 mg/mL of USP Quetiapine Fumarate RS from *Standard stock solution* in *Acid stage medium*

Buffer stage standard solution: 0.03 mg/mL of USP Quetiapine Fumarate RS from *Standard stock solution* in *Buffer stage medium*

Acid stage sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first portion of filtrate if needed. Dilute the filtrate further with *Acid stage medium*, if needed. Replace the portion of solution removed from the vessel with an equivalent volume of warmed *Acid stage medium*.

Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first portion of filtrate if needed. Dilute the filtrate further with *Buffer stage medium*, if needed. Replace the portion of solution removed from the vessel with an equivalent volume of warmed *Buffer stage medium*.

Instrumental conditions

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

Mode: UV

Analytical wavelength: 290 nm

Blank: *Acid stage medium* or *Buffer stage medium*

System suitability

Samples: *Acid stage standard solution* and *Buffer stage standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%, *Acid stage standard solution* and *Buffer stage standard solution*

Analysis

Samples: *Acid stage standard solution* and *Acid stage sample solution* or *Buffer stage standard solution* and *Buffer stage 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):

$$C_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times N$$

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)

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):

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

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

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

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

$$\text{Result}_5 = \{(C_5 \times V_B) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of quetiapine in *Acid stage medium* or *Buffer stage medium* in the portion of sample withdrawn at each time point (mg/mL)

V_A = volume of *Acid stage medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Acid stage sample solution* or *Buffer stage sample solution* withdrawn from the vessel and replaced with *Acid stage medium* or *Buffer stage medium*, respectively (mL)

V_B = volume of *Buffer stage medium*, 1000 mL

Tolerances: See *Table 7*.

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 15
2	4	28–48
3	6	40–60
4	10	62–82
5	16	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 8:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Acid stage medium: Citrate buffer, pH 4.8 (10.5 g/L of citric acid and 3.6 g/L of sodium hydroxide in water; adjust with either a 200-g/L solution of citric acid in water or adjust with 1 N sodium hydroxide VS to obtain a pH of 4.8 ± 0.05, if necessary); 900 mL

0.05 M phosphate buffer solution: 7.1 g/L of anhydrous dibasic sodium phosphate and 18.4 g/L of sodium hydroxide in water

Buffer stage medium: Phosphate buffer, pH 6.6 (add 100 mL of *0.05 M phosphate buffer solution* to *Acid stage medium*; adjust with either a 200-g/L solution of citric acid in water or adjust with 1 N sodium hydroxide VS to obtain a pH of 6.6 ± 0.05, if necessary); 1000 mL

Apparatus 1: 20-mesh basket; 200 rpm

Times: 1 and 4 h in *Acid stage medium*; 10 and 20 h in *Buffer stage medium*. The time in *Buffer stage medium* includes the time in *Acid stage medium*.

Procedure: Run the test in *Acid stage medium* for the times specified. After 5 h, add 100 mL of *0.05 M phosphate buffer solution* and continue running the test in *Buffer stage medium* for the times specified.

Buffer: To each liter of water, add 1 mL of trifluoroacetic acid, and adjust with stronger ammonia water to a pH of 3.0 ± 0.05.

Mobile phase: Methanol and *Buffer* (70:30)

Standard stock solution: 1.2 mg/mL of USP Quetiapine Fumarate RS prepared as follows. Transfer an appropriate amount of USP Quetiapine Fumarate RS into a suitable volumetric flask. Add 24% of the flask volume of methanol and sonicate to dissolve. Dilute with water to volume.

Acid stage standard solution: (*L*/820) mg/mL of USP Quetiapine Fumarate RS from the *Standard stock solution* in *Acid stage medium*, where *L* is the label claim of quetiapine in mg/Tablet. Pass the solution through a suitable filter of 0.2-µm pore size, and discard the first few milliliters of filtrate.

Buffer stage standard solution: (*L*/820) mg/mL of USP Quetiapine Fumarate RS from the *Standard stock solution* in *Buffer stage medium*, where *L* is the label claim of quetiapine in mg/Tablet. Pass the solution through a suitable filter of 0.2-µm pore size, and discard the first few milliliters of filtrate.

Acid stage sample solution: Pass a portion of the solution under test through a suitable filter, and discard the first portion of filtrate. Replace the portion of solution removed from the vessel with an equal volume of *Acid stage medium*.

Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter, and discard the first portion of filtrate. Replace the portion of solution removed from the vessel with an equal volume of *Buffer stage medium*.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 5.0-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 1.0 µL

Run time: NLT 1.7 times the retention time of quetiapine

System suitability

Samples: *Acid stage standard solution* and *Buffer stage standard solution*

Suitability requirements

Tailing factor: NMT 2.0, *Acid stage standard solution* and *Buffer stage standard solution*

Relative standard deviation: NMT 2.0%, *Acid stage standard solution* and *Buffer stage standard solution*

Analysis

Samples: *Acid stage standard solution* and *Acid stage sample solution* or *Buffer stage standard solution* and *Buffer stage sample solution*

Calculate the concentration (C_i) of quetiapine ($C_{21}H_{25}N_3O_2S$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response from the *Acid stage sample solution* or *Buffer stage sample solution*

r_S = peak response from the *Acid stage standard solution* or *Buffer stage standard solution*, corresponding to the related sample solution

C_S = concentration of USP Quetiapine Fumarate RS in the *Acid stage standard solution* or *Buffer stage 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):

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

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

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

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

C_i = concentration of quetiapine in *Acid stage medium* or *Buffer stage medium* in the portion of sample withdrawn at each time point (mg/mL)

V_A = volume of *Acid stage medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Acid stage sample solution* or *Buffer stage sample solution* withdrawn from the vessel and replaced with *Acid stage medium* or *Buffer stage medium*, respectively (mL)

V_B = volume of *Buffer stage medium*, 1000 mL

Tolerances: See *Table 8*.

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved (for 50-mg, 150-mg, and 200-mg Tablets) (%)	Amount Dissolved (for 300-mg and 400-mg Tablets) (%)
1	1	NMT 20	NMT 20
2	4	25–45	30–50
3	10	60–80	65–85
4	20	NLT 80	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*.▲ (TBD)

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

IMPURITIES

Change to read:

- **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 9*▲ (TBD) 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 9*▲ (TBD) 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 9*▲ (TBD)

Acceptance criteria: See ▲*Table 9*.▲ (TBD) Disregard peaks less than 0.05%.

▲Table 9▲ (TBD)

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 degradation products.

[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 degradation products.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **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.

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