Quetiapine Tablets

Type of Posting	Revision Bulletin
Posting Date	25–Sep–2015
Official Date	01–Nov–2015
Expert Committee	Monographs—Chemical Medicines 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Monographs—Chemical Medicines 4 Expert Committee has revised the Quetiapine Tablets monograph. The purpose of the revision is to include a blank solution and clarify the sample preparation for identification by IR.

This Quetiapine Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* of *USP 39–NF 34.*

Should you have any questions, please contact Ravi Ravichandran, Ph.D (301-816-8330, rr@usp.org).

Add the following:

▲Quetiapine Tablets

DEFINITION

Quetiapine Tablets contain an amount of quetiapine fumarate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$).

IDENTIFICATION

Change to read:

- **A. INFRARED ABSORPTION** ⟨197F⟩

  Standard solution: Dissolve 10 mg of quetiapine fumarate in 10 mL of acetone. Sonicate for 10 min. Filter and evaporate the solvent. Dissolve the residue in 2 mL of chloroform. Filter and use 20 µL of the filtrate for analysis.

  Sample solution: Finely powder 10 Tablets. Dissolve an amount of the powder equivalent to 10 mg of quetiapine fumarate in 10 mL of acetone, avoiding large pieces of Tablet coating, if any. Sonicate for 10 min. Filter and evaporate the solvent. Dissolve the residue in 2 mL of chloroform. Filter and use the filtrate for analysis.

  •**Blank:** Filter 10 mL of acetone and evaporate the solvent. Dissolve the residue using 2 mL of chloroform and filter.•

  Analysis

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

  Add drop-wise approximately 20 µL of each of the samples separately onto a clean IR transmission window, allowing each drop to dry before adding the next. Record the spectra.

  Acceptance criteria: Meet the requirements• (RB 1-Nov-2015)

- **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: 1.4 g/L of monobasic potassium phosphate in water. To 1 L of this solution, add 1 mL of triethylamine and adjust with dilute phosphoric acid to a pH of 6.5 (1 in 10, v/v).

  Mobile phase: Acetonitrile and *Buffer* (35:65)

  Standard solution: 0.1 mg/mL of USP Quetiapine Fumarate RS in *Mobile phase*

  Sample stock solution: Nominally 2.0 mg/mL of quetiapine prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask. Add water to fill 5% of the final volume, and sonicate to disperse the Tablets. Add *Mobile phase* to fill 60% of the final volume, and sonicate for 30 min with intermittent shaking. Dilute with *Mobile phase* to volume. Centrifuge for 5 min. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

  Sample solution: Nominally 0.1 mg/mL of quetiapine prepared by diluting an aliquot of the *Sample stock solution* with *Mobile phase*

  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 225 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Flow rate: 1.5 mL/min
  Injection volume: 20 µL
  Run time: 2 times the retention time of quetiapine

  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 1.5
  Relative standard deviation: NMT 2.0%

  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:

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

  r_U = peak response of quetiapine from the *Sample solution*
  r_S = peak response of quetiapine 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)
  N = number of moles of quetiapine/mole of quetiapine fumarate, 2
  M_{r1} = molecular weight of quetiapine free base, 383.51
  M_{r2} = molecular weight of quetiapine fumarate, 883.09

  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

  Test 1
  Medium: Water; 900 mL, deaerated
  Apparatus 2: 50 rpm
  Time: 30 min

  Buffer: 1.4 g/L of monobasic potassium phosphate in water. To 1 L of this solution, add 1 mL of triethylamine and adjust with dilute phosphoric acid to a pH of 6.0 (1 in 10).

  Mobile phase: Acetonitrile and *Buffer* (35:65)

  Standard stock solution: 3.3 mg/mL of USP Quetiapine Fumarate RS prepared as follows. Dissolve the Standard first in methanol using 10% of the final volume, and dilute with *Medium* to volume.

  Standard solution: 0.03 mg/mL of USP Quetiapine Fumarate RS in *Medium* from the *Standard stock solution*

  Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

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

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 2 mL/min
Injection volume: 50 µL
Run time: 1.5 times the retention time of quetiapine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved:

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

r_U = peak response of quetiapine from the *Sample solution*
r_S = peak response of quetiapine from the *Standard solution*
C_S = concentration of USP Quetiapine Fumarate RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
N = number of moles of quetiapine/mole of quetiapine fumarate, 2
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) is dissolved.

Test 2
If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 1 g/L of sodium chloride in water; 900 mL, deaerated
Apparatus 2: 50 rpm
Time: 20 min
Standard stock solution: 1.3 mg/mL of USP Quetiapine Fumarate RS prepared as follows. Transfer a suitable quantity of USP Quetiapine Fumarate RS to a suitable volumetric flask. Dissolve in about 25% of the flask volume of methanol. Dilute with *Medium* to volume.
Standard solution: (*L*/900) mg/mL of USP Quetiapine Fumarate RS from a suitable volume of the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter.
Blank: *Medium*
Instrumental conditions
Mode: UV
Analytical wavelength: 290 nm with background correction at 490 nm
Cell: See *Table 1*.

Table 1

Label claim, *L* (mg/Tablet)	Cell (cm)
25	1.0
50	1.0
100	0.5
150	0.2
200	0.2
300	0.1
400	0.1

Analysis
Samples: *Medium*, *Standard solution*, and *Sample solution*
Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved:

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

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

Tolerances: NLT 80% (*Q*) of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) is dissolved.

Test 3
If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Times
For Tablets labeled to contain 25 mg: 30 min
For Tablets labeled to contain 50, 100, 200, 300, or 400 mg: 45 min
Standard solution: 0.34 mg/mL of USP Quetiapine Fumarate RS in 0.1 N hydrochloric acid
Dilute standard solution: 0.06 mg/mL of USP Quetiapine Fumarate RS from the *Standard solution* in 0.1 N hydrochloric acid
Sample solution: Withdraw a suitable portion of the solution under test. Transfer 9 mL of the portion to a 10-mL volumetric flask and dilute with 1 N hydrochloric acid to volume. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size and discard the first 2 mL.
Instrumental conditions
Mode: UV
Analytical wavelength: 282 nm
Cells
For Tablets labeled to contain 25 or 50 mg: 0.5 cm
For Tablets labeled to contain •100,• (ERR 1-Apr-2015) 200, 300, or 400 mg: 0.1 cm
Blank: 0.1 N hydrochloric acid
Analysis
Samples: *Standard solution, Dilute standard solution, Sample solution*, and *Blank*
For Tablets labeled to contain 25 or 50 mg
Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Dilute standard solution*
C_S = concentration of USP Quetiapine Fumarate RS in the *Dilute standard solution* (mg/mL)

D = dilution factor, 1.1
N = number of moles of quetiapine/mole of quetiapine fumarate, 2
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

For Tablets labeled to contain 100, 200, 300, or 400 mg

Calculate the percentage of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Quetiapine Fumarate RS in the *Standard solution* (mg/mL)
D = dilution factor, 1.1
N = number of moles of quetiapine/mole of quetiapine fumarate, 2
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances

For Tablets labeled to contain 25 mg: NLT 75% (Q) of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) is dissolved.

•**For Tablets labeled to contain 50, 100, 200, 300, or 400 mg:**• (ERR 1-Apr-2015) NLT 70% (Q) of the labeled amount of quetiapine ($C_{21}H_{25}N_3O_2S$) is dissolved.

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

IMPURITIES

- **ORGANIC IMPURITIES**

Buffer: Dissolve 0.8 g of anhydrous dibasic sodium phosphate and 0.6 g of potassium dihydrogen orthophosphate in 1 L of water.

Solution A: Acetonitrile and *Buffer* (10:90). Adjust with dilute phosphoric acid (1 in 10, v/v) to a pH of 6.7.

Solution B: Acetonitrile

Diluent: Acetonitrile and *Solution A* (65:35)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
20	75	25
30	65	35
35	35	65
55	25	75
56	80	20
65	80	20

System suitability solution: 0.5 mg/mL of USP Quetiapine System Suitability RS in *Diluent* prepared as follows. Transfer the required quantity of USP Quetiapine System Suitability RS to a suitable volumetric flask. Add 70% of the flask volume and sonicate to dissolve. Dilute with *Diluent* to volume.

Standard solution: 1.2 µg/mL of USP Quetiapine Fumarate RS in *Diluent*. Sonication may be used to aid in dissolution.

Sample solution: Nominally 0.5 mg/mL of quetiapine in *Diluent* from a portion of weighed and crushed Tablets (NLT 10). Sonicate for 10 min with intermittent shaking.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between quetiapine desthoxy and quetiapine peaks, *System suitability solution*
Tailing factor: NMT 1.5 for the quetiapine peak, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual degradation product in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of quetiapine 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)
N = number of moles of quetiapine/mole of quetiapine fumarate, 2
M_{r1} = molecular weight of quetiapine free base, 383.51
M_{r2} = molecular weight of quetiapine fumarate, 883.09

Acceptance criteria: See *Table 3*. Disregard any peak with an area below 0.05% in the *Sample solution*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Quetiapine *N*-oxide[a]	0.28	0.2
Quetiapine related compound B	0.39	0.2
Quetiapine related compound G	0.69	0.2
Quetiapine desethoxy[b,c]	0.88	—
Quetiapine	1.0	—
Bis(dibenzothiazepinyl) piperazine[b,d]	2.0	—

[a] 4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)-1-[2-(2-hydroxyethoxy)ethyl]piperazine 1-oxide.
[b] Process impurities controlled in the drug substance. Included for identification purposes only. Not reported for the drug product and not included in the total impurities.
[c] 2-[4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.
[d] 1,4-Bis(dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazine.

Table 3 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	0.2
Total impurities	—	0.5

[a] 4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)-1-[2-(2-hydroxyethoxy)ethyl]piperazine 1-oxide.

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

[c] 2-[4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.

[d] 1,4-Bis(dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazine.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and 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 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(10H)-one; and Quetiapine desethoxy: 2-[4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.

▲*USP38*