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 (C21H25N3O2S).

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.

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%
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.)
2 Quetiapine

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 (C₂₁H₂₅N₃O₂S) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_t} \right) \times \frac{C_s \times V \times N \times (M_r/M_m)}{(1/L) \times 100}
\]

\[r_0 = \text{peak response of quetiapine from the Sample solution}\]
\[r_t = \text{peak response of quetiapine from the Standard solution}\]
\[C_s = \text{concentration of USP Quetiapine Fumarate RS in the Standard solution (mg/mL)}\]
\[V = \text{volume of Medium, } 900 \text{ mL}\]
\[N = \text{number of moles of quetiapine/mole of quetiapine fumarate, } 2\]
\[M_r = \text{molecular weight of quetiapine fumarate, } 383.51\]
\[M_m = \text{molecular weight of quetiapine free base, } 383.09\]
\[L = \text{label claim (mg/Tablet)}\]

Tolerances: NLT 80% (Q) of the labeled amount of quetiapine (C₂₁H₂₅N₃O₂S) 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>
<thead>
<tr>
<th>Label claim, L (mg/Tablet)</th>
<th>Cell (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.0</td>
</tr>
<tr>
<td>50</td>
<td>1.0</td>
</tr>
<tr>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>200</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Analysis
Samples: Medium, Standard solution, and Sample solution
Calculate the percentage of the labeled amount of quetiapine (C₂₁H₂₅N₃O₂S) dissolved:

\[
\text{Result} = \left( \frac{A_0}{A_t} \right) \times C_s \times D \times N \times (M_r/M_m) \times V \times (1/L) \times 100
\]

\[A_0 = \text{absorbance of the Sample solution}\]
\[A_t = \text{absorbance of the Dilute solution}\]
\[C_s = \text{concentration of USP Quetiapine Fumarate RS in the Dilute standard solution (mg/mL)}\]
$D = \text{dilution factor, 1.1}$

$N = \text{number of moles of quetiapine/mole of quetiapine fumarate, 2}$

$M_1 = \text{molecular weight of quetiapine free base, 383.51}$

$M_2 = \text{molecular weight of quetiapine fumarate, 883.09}$

$V = \text{volume of Medium, 900 mL}$

System suitability solution:

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:

$$\text{Result} = \left(\frac{A_0}{A_1}\right) \times C_s \times D \times N \times \left(\frac{M_1}{M_2}\right) \times V \times \left(\frac{1}{L}\right) \times 100$$

$A_0 = \text{absorbance of the Sample solution}$

$A_1 = \text{absorbance of the Standard solution}$

$C_s = \text{concentration of USP Quetiapine Fumarate RS in the Standard solution (mg/mL)}$

$D = \text{dilution factor, 1.1}$

$N = \text{number of moles of quetiapine/mole of quetiapine fumarate, 2}$

$M_1 = \text{molecular weight of quetiapine free base, 383.51}$

$M_2 = \text{molecular weight of quetiapine fumarate, 883.09}$

$V = \text{volume of Medium, 900 mL}$

$L = \text{label claim (mg/Tablet)}$

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:

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>30</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>55</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>56</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>65</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

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. Sonicate 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:

$$\text{Result} = \left(\frac{r_U r_S}{r_U r_S + r_S}ight) \times \left(\frac{C_s}{C_0}ight) \times N \times \left(\frac{M_1}{M_2}\right) \times 100$$

$r_U = \text{peak response of each individual impurity from the Sample solution}$

$r_S = \text{peak response of quetiapine from the Standard solution}$

$C_s = \text{concentration of USP Quetiapine Fumarate RS in the Standard solution (mg/mL)}$

$C_0 = \text{nominal concentration of quetiapine in the Sample solution (mg/mL)}$

$N = \text{number of moles of quetiapine/mole of quetiapine fumarate, 2}$

$M_1 = \text{molecular weight of quetiapine free base, 383.51}$

$M_2 = \text{molecular weight of quetiapine fumarate, 883.09}$

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

Table 3

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine $N$-oxide</td>
<td>0.28</td>
<td>0.2</td>
</tr>
<tr>
<td>Quetiapine related compound B</td>
<td>0.39</td>
<td>0.2</td>
</tr>
<tr>
<td>Quetiapine related compound G</td>
<td>0.69</td>
<td>0.2</td>
</tr>
<tr>
<td>Quetiapine desethoxy</td>
<td>0.88</td>
<td>—</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Bis(dibenzo[6,7]thiazepinyl)piperazine</td>
<td>2.0</td>
<td>—</td>
</tr>
</tbody>
</table>

*4-(2-Hydroxyethyl)ethyl|piperazine 1-oxide.

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.

2-(2-Hydroxyethoxy)ethyl|piperazine 1-oxide.

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**Table 3 (Continued)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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

Useful impurities controlled in the drug substance. Included for identification purposes only. Not reported for the drug product and not included in the total impurities.

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

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)dibenzob[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