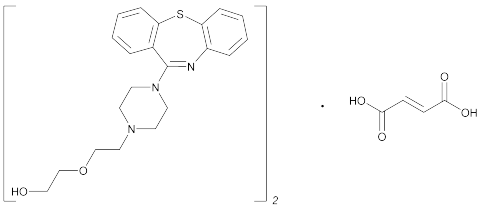
Quetiapine Fumarate



$(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$ 883.09

Ethanol, 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-, (*E*)-2-butenedioate (2:1) (salt); 2-[2-(4-Dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl) ethoxy]ethanol fumarate (2:1) (salt) CAS RN®: 111974-72-2; UNII: 2S3PL1B6UJ.

DEFINITION

Quetiapine Fumarate contains NLT 98.0% and NMT 102.0% of quetiapine fumarate $[(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4]$, calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A. ▲Spectroscopic Identification Tests** ⟨197⟩**,** *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)
- **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: 2.6 g/L of dibasic ammonium phosphate. Adjust with phosphoric acid to a pH of 6.5.
Mobile phase: Methanol, acetonitrile, and *Buffer* (54:7:39)
System suitability solution: 1.0 mg/mL of USP Quetiapine System Suitability RS in *Mobile phase*
Standard stock solution: 0.16 mg/mL of USP Quetiapine Fumarate RS in *Mobile phase*
Standard solution: 0.08 mg/mL of USP Quetiapine Fumarate RS from *Standard stock solution* in *Mobile phase*
Sample stock solution: 0.16 mg/mL of Quetiapine Fumarate in *Mobile phase*
Sample solution: 0.08 mg/mL of Quetiapine Fumarate from *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: 50 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for quetiapine desethoxy and quetiapine are about 0.9 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.5 between the quetiapine desethoxy and quetiapine peaks, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of quetiapine fumarate $[(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4]$ in the portion of Quetiapine Fumarate taken:

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

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 = concentration of Quetiapine Fumarate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Organic Impurities**

Buffer: 3.1 g/L of ammonium acetate in water. Add 2 mL of 25% ammonium hydroxide to each 1 L of solution. The pH of the resulting solution is NLT 9.2.
Solution A: Acetonitrile and *Buffer* (25:75)
Solution B: Acetonitrile
Diluent: *Solution A* and *Solution B* (86:14)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
25	100	0
60	29.3	70.7
60.1	100	0
68	100	0

Peak identification solution: 1 µg/mL of USP Quetiapine Fumarate RS, 10 µg/mL of USP Quetiapine Related Compound B RS, and 2 µg/mL of USP Quetiapine Related Compound G RS in *Diluent*
System suitability solution: 1 mg/mL of USP Quetiapine System Suitability RS in *Diluent*
Standard solution: 0.001 mg/mL of USP Quetiapine Fumarate RS in *Diluent*
Sample solution: 1.0 mg/mL of Quetiapine Fumarate in *Solution A*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L7
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Samples: *Peak identification solution, System suitability solution,* and *Standard solution*
[NOTE—See *Table 2* for relative retention times. Quetiapine related compound B will be the largest peak in the *Peak identification solution* chromatogram.]
Suitability requirements
Resolution: NLT 4.0 between the quetiapine desethoxy and quetiapine peaks, *System suitability solution*; NLT 3.0 between quetiapine related compound B and quetiapine related compound G, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Quetiapine Fumarate taken:

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

r_U = peak response of each 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 = concentration of Quetiapine Fumarate in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard peaks below 0.05% or with retention times less than 2 min.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fumaric acid[a]	0.08	—	—
Quetiapine quaternary salt[b, c]	0.27	0.62	0.15
Quetiapine related compound G	0.55	1.2	0.15
Quetiapine related compound B	0.67	1.2	0.15
Quetiapine desethoxy[d]	0.83	1.0	0.15
Quetiapine	1.0	—	—
Quetiapine tetraethylene glycol analog[b, e]	1.2	1.0	0.10
N-Ethyl quetiapine[b, f]	1.51	1.1	0.15
Bis(dibenzothiazepinyl) piperazine[b, g]	2.22	1.0	0.10
Any other unknown individual impurity	—	—	0.10
Total impurities	—	—	0.50

[a] Peak due to counter ion, included for peak identification purposes. Not to be included in total impurities.
[b] Process impurity specific to manufacturing process.
[c] 4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)-1,1-bis[2-(2-hydroxyethoxy)ethyl] piperazin-1-ium.
[d] 2-[4-(Dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.
[e] 2-[2-(2-{2-[4-(Dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy}ethoxy) ethoxy]ethanol.
[f] 11-(4-Ethylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.
[g] 1,4-Bis(dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazine.

SPECIFIC TESTS

- **Loss on Drying** ⟨731⟩
  Analysis: Dry at 105° to constant weight.
  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light.
- **USP Reference Standards** ⟨11⟩
  USP Quetiapine Fumarate RS
  USP Quetiapine Related Compound B RS
  11-(Piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.
  $C_{17}H_{17}N_3S$ 295.40
  USP Quetiapine Related Compound G RS
  Dibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one.
  $C_{13}H_9NOS$ 227.28
  USP Quetiapine System Suitability RS
  It contains quetiapine fumarate and NLT 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.