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Mirtazapine Tablets

DEFINITION

Mirtazapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$).

IDENTIFICATION

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

Extraction mixture: *n*-Hexane and water (1:1)

Sample: Transfer an amount equivalent to 30 mg of mirtazapine from finely powdered Tablets to a suitable centrifuge tube. Add *Extraction mixture* to obtain a solution of 1 mg/mL of mirtazapine in *n*-hexane. Shake for 5 min, and centrifuge. Decant, and evaporate the supernatant.

Standard: Dissolve USP Mirtazapine RS in *Extraction mixture* to obtain a solution having a concentration of about 1 mg/mL of mirtazapine in *n*-hexane. Shake for 5 min, and centrifuge. Decant, and evaporate the supernatant.

• **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**

Diluent: Acetonitrile and water (1:1)

Buffer: Dissolve 18.0 g of tetramethylammonium hydroxide pentahydrate in 950 mL of water. Adjust with phosphoric acid to a pH of 7.4, and dilute with water to 1 L.

Mobile phase: Acetonitrile, methanol, tetrahydrofuran, and *Buffer* (15:12.5:7.5:65)

Standard solution: 0.3 mg/mL of USP Mirtazapine RS in *Diluent*

Sample solution: Nominally 0.3 mg/mL of mirtazapine (from an amount equivalent to the weight of 1 Tablet from NLT 20 finely powdered Tablets) in *Diluent*. Shake vigorously for 10 min, centrifuge an aliquot, and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 7000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) in the portion of Tablets 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 Mirtazapine RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.

Standard solution: USP Mirtazapine RS in *Medium* in a concentration similar to the one expected in the *Sample solution*

Instrumental conditions

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

Mode: UV

Analytical wavelength: 315 nm

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Mirtazapine RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

Diluent, Buffer, and **Mobile phase:** Proceed as directed in the *Assay*.

System suitability solution: 1.5 mg/mL of USP Mirtazapine Resolution Mixture RS in *Diluent*

Standard solution: 0.015 mg/mL of USP Mirtazapine RS in *Diluent*

Sample solution: 1.5 mg/mL of mirtazapine (from an amount equivalent to the weight of 1 Tablet from NLT 20 finely powdered Tablets) in *Diluent*. Shake vigorously for 10 min, centrifuge an aliquot, and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of mirtazapine

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—The relative retention times are listed in *Table 1*.]

Suitability requirements

Resolution: NLT 1.5 between acyclomirtazapine methyl derivative (impurity E) and ▲10-ketomirtazapine▲ (ERR 1-Mar-2023) (impurity F), *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of any impurity from the *Sample solution*

r_S = mirtazapine peak response from the *Standard solution*

C_S = concentration of USP Mirtazapine RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of the *Sample solution* (mg/mL)

F = relative response factor for the corresponding impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mirtazapine *N*-oxide[a]	0.2	0.8	0.2
Acyclomirtazapine alcohol[b,g]	0.3	—	—
▲1-Ketomirtazapine▲ (ERR 1-Mar-2023) [c]	0.35	1.0	0.2
Desmethylmirtazapine[d,g]	0.4	—	—
Mirtazapine	1.0	—	—
Acyclomirtazapine methyl derivative[e,g]	1.3	—	—
10-Ketomirtazapine[f]	1.35	5.0	0.2
Any individual unspecified degradation product	—	1.0	0.2
Total impurities	—	—	2.0

[NOTE—Disregard any peak representing less than 0.05% of the main peak and any peak that is due to the *Diluent*.]

[a] 1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide. (Impurity A)

[b] (2-(4-Methyl-2-phenylpiperazin-1-yl)pyridin-3-yl)methanol. (Impurity B)

[c] (2-Methyl-3,4,10,14b-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-1(2*H*)-one. (Impurity C)

[d] 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine. (Impurity D)

[e] 4-Methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine. (Impurity E)

[f] 2-Methyl-1,2,3,4-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-10(14b*H*)-one. (Impurity F)

[g] Process impurity. Included for identification purposes only. Not to be included in *Total impurities*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Mirtazapine RS

USP Mirtazapine Resolution Mixture RS

Mirtazapine.

Impurity A: 1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide.
Impurity B: (2-(4-Methyl-2-phenylpiperazin-1-yl)pyridin-3-yl)methanol.
Impurity C: (2-Methyl-3,4,10,14b-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-1(2*H*)-one.
Impurity D: [NOTE—This impurity may be available either as the free base form or as the hydrochloride salt form.] 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine or 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine hydrochloride.
Impurity E: 4-Methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine.
Impurity F: 2-Methyl-1,2,3,4-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-10(14b*H*)-one.

Topic/Question	Contact	Expert Committee
MIRTAZAPINE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

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