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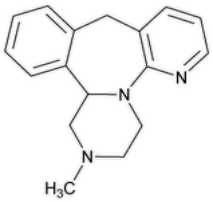
Mirtazapine



$C_{17}H_{19}N_3$ 265.35

Pyrazino[2,1-*a*]pyrido[2,3-c][2]benzazepine,1,2,3,4,10,14b-hexahydro-2-methyl-;

1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-c][2]-benzazepine CAS RN®: 85650-52-8; UNII: A051Q2099Q.

DEFINITION

Mirtazapine contains NLT 98.0% and NMT 102.0% of mirtazapine ($C_{17}H_{19}N_3$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
- **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 g of tetramethylammonium hydroxide pentahydrate in 950 mL of water. Adjust with phosphoric acid to a pH of 7.4. 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: 0.3 mg/mL of Mirtazapine in *Diluent*

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 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of mirtazapine ($C_{17}H_{19}N_3$) in the portion of Mirtazapine 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 = concentration of Mirtazapine in the *Sample solution* (mg/mL)

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

IMPURITIES

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

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

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

Standard solution: 0.0015 mg/mL of USP Mirtazapine RS in *Diluent*

Sample solution: 1.5 mg/mL of Mirtazapine in *Diluent*

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: Twice 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 (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 Mirtazapine 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 = peak response of mirtazapine from the *Standard solution*

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

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

F = relative response factor (see *Table 1*)

[Note—Disregard any peak with a result of 0.05% or less, as calculated using the formula given above.]

Acceptance criteria: See *Table 1*.

Table 1

Impurity Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mirtazapine *N*-oxide[a]	0.2	0.8	0.1
Acyclomirtazapine alcohol[b]	0.3	0.8	0.1
1-Ketomirtazapine[c]	0.35	1.0	0.1
Desmethylmirtazapine[d]	0.4	1.0	0.1
Mirtazapine	1.0	—	—

Impurity Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Acyclomirtazapine methyl derivative[e]	1.3	1.0	0.1
10-Ketomirtazapine[f]	1.35	5.0	0.1
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.5

[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).

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨921⟩**:** NMT 3.5%
- **OPTICAL ROTATION,** *Specific Rotation* ⟨781S⟩

Sample solution: 10 mg/mL, in denatured alcohol

Acceptance criteria: +2° to −2°

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** Label it to indicate whether it is anhydrous or hemihydrate.

Change to read:

- **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.]▲ (ERR 1-Apr-2021)

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.▲ (ERR 1-Apr-2021)

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.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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

Chromatographic Database Information: Chromatographic Database

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