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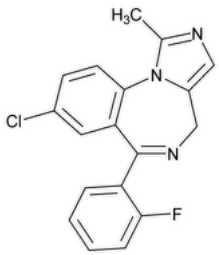
Midazolam



$C_{18}H_{13}ClFN_3$ 325.77

4-*H*-Imidazo[1,5-*a*][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl;

8-Chloro-6-(*o*-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine CAS RN®: 59467-70-8; UNII: R60L0SM5BC.

DEFINITION

Midazolam contains NLT 98.5% and NMT 101.5% of $C_{18}H_{13}ClFN_3$, 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: 7.7 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 5.5 ± 0.1.

Mobile phase: Acetonitrile and *Buffer* (1:2)

Standard solution: 0.04 mg/mL of USP Midazolam RS in *Mobile phase*

Sample solution: 0.04 mg/mL of Midazolam in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L60

Flow rate: 1.5 mL/min

Injection size: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 10,000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{18}H_{13}ClFN_3$ in the portion of Midazolam 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 Midazolam RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.5%–101.5% on the dried basis

IMPURITIES

Inorganic Impurities

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

Organic Impurities

- **Procedure**

Buffer, Mobile phase, Standard solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity check solution: Dilute the *Standard solution* with *Mobile phase* to obtain a 0.2-µg/mL solution.

Sample solution: 0.2 mg/mL of Midazolam in *Mobile phase*

System suitability

Samples: *Standard solution* and *Sensitivity check solution*

Suitability requirements

Column efficiency: NLT 10,000 theoretical plates, *Standard solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Peak ratio: The ratio of the area of the midazolam peak of the *Standard solution* to the area of the midazolam peak of the *Sensitivity check solution* should be within 160–240.

Analysis

Sample: *Sample solution*

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

$$\text{Result} = (r_U/F)/[\Sigma(r_U/F) + r_T] \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_T = peak response of Midazolam from the *Sample solution*

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

Acceptance criteria: See *Impurity Table 1*.

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Reduced midazolam[a]	0.20	1.0	0.1
Reduced reduced midazolam[b]	0.24	1.0	0.1
Amino compound[c]	0.25	0.5	0.1
Oxide midazolam[d]	0.46	1.3	0.1
Nitromethylene compound[e]	0.76	1.0	0.1
Dihydromidazolam[f]	0.83	0.5	0.1
Midazolam	1.0	—	—
Desfluoromidazolam[g]	1.14	1.0	0.2
6*H*-isomer[h]	2.48	0.7	0.1
Unknown impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] 8-Chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3*H*-imidazo[1,5-a][1,4]-benzodiazepine.

[b] 8-Chloro-6-(2-fluorophenyl)-3a,4,5,6-tetrahydro-1-methyl-3*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

[c] 2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine.

[d] 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-5-oxide.

[e] 7-Chloro-1,3-dihydro-2-nitromethylene-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepine-4-oxide.

[f] 8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

[g] 8-Chloro-6-phenyl-1-methyl-4*H*-imidazo-[1,5-*a*][1,4]-benzodiazepine.

[h] 8-Chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1,5-*a*][1,4]-benzodiazepine.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩:** Dry a sample at 105° for 2 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

• **USP Reference Standards ⟨11⟩**
USP Midazolam RS

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

Topic/Question	Contact	Expert Committee
MIDAZOLAM	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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