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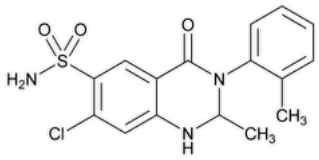
Metolazone



$C_{16}H_{16}ClN_3O_3S$ 365.83

6-Quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-;

7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide CAS RN®: 17560-51-9; UNII: TZ7V40X7VX.

DEFINITION

Metolazone contains NLT 97.0% and NMT 102.0% of metolazone ($C_{16}H_{16}ClN_3O_3S$), calculated on the dried basis.

IDENTIFICATION

- **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**
- **B.** **Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**

  Sample solution: 5 µg/mL in methanol

  Acceptance criteria: Meets the requirements
- **C.** 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**

Protect all solutions of Metolazone from light.

Buffer: 5.4 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile, methanol, and *Buffer* (10:25:65)

Standard stock solution: 0.5 mg/mL of USP Metolazone RS in tetrahydrofuran

Standard solution: 0.05 mg/mL of USP Metolazone RS in alcohol from the *Standard stock solution*

Sample stock solution: 1 mg/mL of Metolazone in tetrahydrofuran

Sample solution: 0.05 mg/mL of Metolazone in alcohol from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 10-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 15 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.4

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of metolazone ($C_{16}H_{16}ClN_3O_3S$) in the portion of sample taken:

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

r_U = peak response of metolazone from the *Sample solution*

r_S = peak response of metolazone from the *Standard solution*

C_S = concentration of USP Metolazone RS in the *Standard solution* (µg/mL)

C_U = concentration of Metolazone in the *Sample solution* (µg/mL)

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

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

Change to read:

• **Organic Impurities**

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

Standard stock solution: 0.48 mg/mL of USP Metolazone RS in tetrahydrofuran

Standard solution: 6 µg/mL of USP Metolazone RS in alcohol from the *Standard stock solution*

Sample solution: 0.6 mg/mL of Metolazone, prepared as follows. Dissolve a suitable amount of Metolazone with tetrahydrafuran in 50% of the total volume, and dilute with alcohol to volume.

Chromatographic system: Proceed as directed in the *Assay*, except for the following:

Column: 4.6-mm × 25-cm; 5-µm packing ▲L1▲ (ERR 1-Mar-2024)

Run time: NLT 3.5 times the retention time of metolazone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.4

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of sample taken:

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

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

r_S = peak response of metolazone from the *Standard solution*

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

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

F = relative response factor of each individual impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desmethyl metolazone[a]	0.7	1.0	0.5
Metolazone benzamide analog[b]	0.8	0.83	0.5
Metolazone	1.0	1.0	—
meta-Metolazone[c]	1.3	0.91	0.5
para-Metolazone[d]	1.4	0.91	0.5
Didehydrometolazone[e]	1.5	0.83	0.5
Any other individual impurity	—	—	0.10
Total impurities[f]	—	—	1.0

[a] 7-Chloro-2-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydroquinazoline-6-sulfonamide.

[b] 2-Amino-4-chloro-5-sulfamoyl-*N*-(*o*-tolyl)benzamide.

[c] 7-Chloro-2-methyl-4-oxo-3-(*m*-tolyl)-1,2,3,4-tetrahydroquinazoline-6-sulfonamide.

[d] 7-Chloro-2-methyl-4-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroquinazoline-6-sulfonamide.

[e] 7-Chloro-2-methyl-4-oxo-3-(*o*-tolyl)-3,4-dihydroquinazoline-6-sulfonamide.

[f] Sum of all individual impurities. Disregard any peaks less than 0.05%.

SPECIFIC TESTS

- **Loss on Drying ⟨731⟩**

  Analysis: Dry a sample at 105° for 2 h.

  Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **USP Reference Standards ⟨11⟩**

  USP Metolazone RS

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

Topic/Question	Contact	Expert Committee
METOLAZONE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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