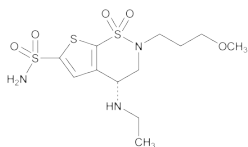


Brinzolamide



$C_{12}H_{21}N_3O_5S_3$ 383.51
 2*H*-Thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide, 4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-, 1,1-dioxide, (*R*)-; (*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide [138890-62-7].

DEFINITION

Brinzolamide contains NLT 98.0% and NMT 102.0% of brinzolamide ($C_{12}H_{21}N_3O_5S_3$), calculated on the dried basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** <197K>
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in *Limit of Brinzolamide Related Compound A*.

ASSAY

PROCEDURE

Buffer: Add 4.0 mL of triethylamine to 1000 mL of water, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Standard solution: 0.1 mg/mL of USP Brinzolamide RS in *Mobile phase*

Sample solution: 0.1 mg/mL of Brinzolamide in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5- μ m packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1200 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of brinzolamide ($C_{12}H_{21}N_3O_5S_3$) in the portion of Brinzolamide 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 Brinzolamide RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

- RESIDUE ON IGNITION** <281>: NMT 0.1%

Delete the following:

- HEAVY METALS**, *Method II* <231>: NMT 20 ppm • (Official 1-

Change to read:

LIMIT OF BRINZOLAMIDE RELATED COMPOUND A

Mobile phase: Dehydrated alcohol, \blacktriangle chromatographic hexane, \blacktriangle USP38 methanol, and diethylamine (55:40:5:0.2)

System suitability solution: 0.4 mg/mL of USP Brinzolamide RS and 0.02 mg/mL of USP Brinzolamide Related Compound A RS in dehydrated alcohol

Sample solution: 0.5 mg/mL of Brinzolamide in dehydrated alcohol

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; packing L51

Flow rate: 0.75 mL/min

Injection volume: 5 μ L

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for brinzolamide and brinzolamide related compound A are 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.8 between brinzolamide and brinzolamide related compound A peaks

Column efficiency: NLT 2000 theoretical plates for the brinzolamide peak

Tailing factor: NMT 1.8 for the brinzolamide peak

Analysis

Sample: *Sample solution*

Calculate the percentage of brinzolamide related compound A in the portion of Brinzolamide taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for brinzolamide related compound A

r_T = sum of the peak responses for brinzolamide and brinzolamide related compound A

Acceptance criteria: NMT 0.5%

ORGANIC IMPURITIES

Buffer: Prepare as directed in the *Assay*.

Mobile phase A: Prepare as directed for *Mobile phase* in the *Assay*.

Mobile phase B: Acetonitrile and *Buffer* (35:65)

System suitability solution: 0.1 mg/mL each of USP Brinzolamide RS and USP Brinzolamide Related Compound B RS in *Mobile phase A*

Sample solution: 1 mg/mL of Brinzolamide in *Mobile phase A*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5- μ m packing L1

Flow rate: 1.0 mL/min

Injection volume: 10 μ L

System suitability

Sample: *System suitability solution*

Use *Mobile phase A*.

[NOTE—The relative retention times for brinzolamide related compound B and brinzolamide are 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the brinzolamide and brinzolamide related compound B peaks

Column efficiency: NLT 1200 theoretical plates for the brinzolamide peak

Tailing factor: NMT 2.0 for the brinzolamide peak

Analysis 1

Use *Mobile phase A*.

Sample: *Sample solution*

Allow the elution to continue for 20 min, and measure the areas for all the peaks, excluding the peaks of *Mobile phase A*.

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

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity

r_T = sum of all the peak responses

Acceptance criteria 1: NMT 0.3% for any individual impurity

Analysis 2

Use *Mobile phase B*.

Sample: *Sample solution*

Allow the elution to continue for 20 min, and measure the areas for brinzolamide and all the peaks having a relative retention greater than 6.

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

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity

r_T = sum of all the peak responses

Acceptance criteria 2: NMT 0.3% for any individual impurity; NMT 1.0% for total impurities from *Analysis 1* and *Analysis 2*

SPECIFIC TESTS**• LOSS ON DRYING** (731)

Analysis: Dry under vacuum at 100°–105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• PACKAGING AND STORAGE: Preserve in well-closed containers.

• USP REFERENCE STANDARDS (11)

USP Brinzolamide RS

USP Brinzolamide Related Compound A RS

Brinzolamide (*S*)-isomer.

$C_{12}H_{21}N_3O_5S_3$ 383.52

USP Brinzolamide Related Compound B RS

(*R*-4-Amino)-2,3-dihydro-2-(3-methoxypropyl)-4*H*-thieno[3,2-*e*]-thiazine-6-sulfonamide-1,1-dioxide ethandioate 1:1.

$C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ 445.49

Mobile phase: Methanol and *Buffer* (35:65)

Standard solution A: 0.2 mg/mL of USP Brinzolamide RS in *Mobile phase*

System suitability solution: 0.06 mg/mL of USP Brinzolamide Related Compound B RS in *Standard solution A*

Sample solution: Nominally 0.2 mg/mL of brinzolamide in *Mobile phase* prepared as follows. Transfer a volume of Ophthalmic Suspension, equivalent to 10 mg of brinzolamide, into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-μm packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 μL

System suitability

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

[NOTE—The relative retention times for brinzolamide related compound B are between 0.48 and 0.61, and the relative retention time for brinzolamide is 1.0.]

Suitability requirements

Resolution: NLT 4.5 between the brinzolamide and brinzolamide related compound B peaks, *System suitability solution*

▲^{USP38}

Tailing factor: NMT 2.0, *System suitability solution*

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

Analysis

Samples: *Standard solution A* and *Sample solution*

Calculate the percentage of the labeled amount of brinzolamide ($C_{12}H_{21}N_3O_5S_3$) in the portion of Ophthalmic Suspension 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 *Standard solution A*

C_S = concentration of USP Brinzolamide RS in *Standard solution A* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES**Change to read:****• LIMIT OF BRINZOLAMIDE RELATED COMPOUND A**

Mobile phase: Dehydrated alcohol, ▲^{USP38}chromatographic hexane, ▲^{USP38} methanol, and diethylamine (55: 40: 5: 0.2)

System suitability solution: 0.4 mg/mL of USP Brinzolamide RS and 0.02 mg/mL of USP Brinzolamide Related Compound A RS in dehydrated alcohol

Sample solution: Transfer a volume of Ophthalmic Suspension, equivalent to 10 mg of brinzolamide, to a 25-mL volumetric flask. Dilute with alcohol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; packing L51

Flow rate: 0.75 mL/min

Injection volume: 5 μL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for brinzolamide and brinzolamide related compound A are 1.0 and

Brinzolamide Ophthalmic Suspension**DEFINITION**

Brinzolamide Ophthalmic Suspension is a sterile, aqueous suspension of Brinzolamide containing a suitable antimicrobial preservative. It contains NLT 90.0% and NMT 110.0% of the labeled amount of brinzolamide ($C_{12}H_{21}N_3O_5S_3$).

IDENTIFICATION

• A. The retention time of the major peak of the *Sample solution* corresponds to that of *Standard solution A*, as obtained in the *Assay*.

ASSAY**Change to read:****• PROCEDURE**

Buffer: 11.75 g/L of ammonium acetate in water. Adjust with acetic acid to a pH of 5.2.