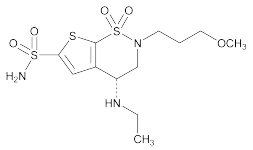
Brinzolamide



$C_{12}H_{21}N_3O_5S_3$ 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-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 20 µL
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, ▲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: 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 µL
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-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 10 µL
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*.

USP Monographs

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

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.
  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, ▲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