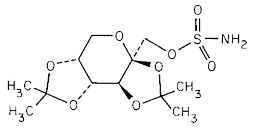
ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and avoid exposure to excessive heat.

Topiramate



$C_{12}H_{21}NO_8S$ 339.36

β-D-Fructopyranose, 2,3:4,5-bis-*O*-(1-methylethylidene)-, sulfamate;

2,3:4,5-Di-*O*-isopropylidene-*β*-D-fructopyranose sulfamate [97240-79-4].

DEFINITION

Topiramate contains NLT 98.0% and NMT 102.0% of $C_{12}H_{21}NO_8S$, calculated on the anhydrous basis.

[**CAUTION—**Great care must be exercised in handling Topiramate because it is a suspected teratogen.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**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**

Mobile phase: Acetonitrile and water (1:1)

Standard solution: 2 mg/mL of USP Topiramate RS in *Mobile phase*

Sample solution: 2 mg/mL of Topiramate in *Mobile phase*

Chromatographic system

(See *Chromatography* ⟨621⟩.)

Mode: LC

Detector: Refractive index

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

Temperature

Column: 50°

Detector 50°

Flow rate: 0.6 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1500 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{12}H_{21}NO_8S$ in the portion of Topiramate 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 Topiramate RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.2%

Delete the following:

•• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** 10 ppm• (Official 1-Jan-2018)

Organic Impurities

[NOTE—On the basis of the synthetic route, perform either *Procedure 2* or *Procedure 3*. If *N*-methyltopiramate is a potential related compound, *Procedure 1* or *Procedure 3* is recommended.]

- **PROCEDURE 1**

Identification solution: 0.2 mg/mL of USP Topiramate Related Compound A RS in methanol

Standard solution A: 40 mg/mL of USP Topiramate RS in methanol

Standard solution B: 0.08 mg/mL of Topiramate from *Standard solution A* and methanol

Standard solution C: 0.04 mg/mL of Topiramate from *Standard solution A* and methanol

Sample solution: 40 mg/mL of Topiramate in methanol

Chromatographic system

(See *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.20-mm layer of chromatographic silica gel mixture, prewashed with methanol and air dried

Application volume: 20 µL

Developing solvent system: Acetonitrile, methanol, and 0.5 M sodium chloride (7:3:10)

Spray reagent: Prepare a 30-mg/mL solution of phenol in alcohol and concentrated sulphuric acid (95:5).

Analysis

Samples: *Standard solution B*, *Standard solution C*, and *Sample solution*

Proceed as directed in the chapter. After elution, air-dry the plate, spray the plate with the *Spray reagent*, and let the plate air-dry. Then dry the plate for 10 min in an oven at 125°. [NOTE—The approximate R_F values for topiramate and topiramate related compound A are 0.65 and 0.70, respectively. Disregard any spots at the origins of the chromatograms. Disregard any spot corresponding to topiramate related compound A because this impurity should be quantified using *Procedure 2*.] Examine the plate using visible light, and estimate the percentage of all secondary spots in the chromatogram of the *Sample solution* by comparing each spot with the principal spot from the chromatograms of the *Standard solutions*.

Acceptance criteria: Any single spot is not greater in size and intensity than the spot for *Standard solution C;* NMT 0.1% of any individual impurity is found; and NMT 0.5% of total impurities by TLC is found.

- **PROCEDURE 2**

Mobile phase: Proceed as directed in the *Assay*. [NOTE—Prepare all solutions fresh before use.]

Sample solution: 40 mg/mL of Topiramate, in *Mobile phase.* [NOTE—Sonication may be used to aid dissolution.]

System suitability solution: 0.3 mg/ml each of USP Fructose RS and USP Topiramate Related Compound A RS, in the *Sample solution*

USP Monographs

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index detector
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperature
Column: 55°
Detector: 55°
Flow rate: 0.6 mL/min
Injection size: 50 µL
Run time: NLT 5 times the retention time of the topiramate peak
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for fructose, topiramate related compound A, and topiramate are 0.45, 0.9, and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.0 between topiramate related compound A and topiramate
Relative standard deviation: NMT 2.0% for the topiramate peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each of the impurities in the portion of Topiramate taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak area of any impurity
r_T = sum of the areas of all of the impurities peaks and the topiramate peak
F = relative response factor, 1.2 for topiramate related compound A and 1.0 for all the other peaks
Acceptance criteria: See *Impurity Table 1*.
Total impurities: NMT 0.5%

Impurity Table 1

Name	Acceptance Criteria, NMT (%)
Fructose	0.3
Topiramate related compound A	0.3
Individual unknown	0.1

- **PROCEDURE 3**
Mobile phase: Methanol and water (16:34)
Standard solution: 10 mg/mL of USP Topiramate RS and 0.04 mg/mL of USP Topiramate Related Compound A RS in *Mobile phase*
Sample solution: 10 mg/mL of Topiramate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 15-cm; 5-µm packing L15
Column temperature: 35°.
Flow rate: 1.5 mL/min
Injection size: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 1.0 between topiramate related compound A and topiramate
Relative standard deviation: NMT 2.0% for the topiramate peak for six replicate injections
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each of the impurities in the portion of Topiramate taken:

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

r_U = peak area of any impurity from the *Sample solution*
r_S = peak area of topiramate from the *Standard solution*
C_S = concentration of USP Topiramate RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)
F = relative response factor, 1.1 for topiramate related compound A and 1.0 for all the other peaks
Acceptance criteria
Topiramate related compound A: NMT 0.3%
Any other individual impurity: NMT 0.10%
Total impurities detected by *Procedure 3*: NMT 0.5%

SPECIFIC TESTS

- **OPTICAL ROTATION,** *Specific Rotation* ⟨**781S**⟩**:** −28.6° to −35.0°, measured at 20°
Sample solution: 4–10 mg/mL, in methanol
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 0.5%
- **LIMIT OF SULFAMATE AND SULFATE**
[NOTE—Use water with resistivity NLT 18 megohm-cm for preparation of *Mobile phase*, *Standard solution*, and *Sample solution*.]
Buffer: 0.8 g/L of *p*-hydroxybenzoic acid in water
Mobile phase: Methanol and *Buffer* (2.5:97.5). Adjust with sodium hydroxide solution to a pH of 9.4 ± 0.5.
Standard solution: 4.5 µg/mL of sodium sulfate and 3.0 µg/mL of sulfamic acid in *Mobile phase* from anhydrous sodium sulfate and sulfamic acid, respectively
Sample solution: 6.0 mg/mL of topiramate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Conductivity
Column: 4.6-mm × 15-cm; 5-µm packing L47
Detector temperature: 30°
Flow rate: 1.5 mL/min
[NOTE—A suitable background suppression unit may be used.]
Injection size: 70 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention time of the sulfamate peak is 0.44 relative to the sulfate peak.]
Suitability requirements
Relative standard deviation: NMT 15.0% for the sulfamate and sulfate peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of sulfate ions in the portion of Topiramate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of sulfate ion from the *Sample solution*
r_S = peak response of sulfate ion from the *Standard solution*
C_S = concentration of sodium sulfate in the *Standard solution* (mg/mL)
C_U = concentration of Topiramate in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of the sulfate anion, 96.04
M_{r2} = molecular weight of anhydrous sodium sulfate, 142.04
Calculate the percentage of sulfamate ions in the portion of Topiramate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of the sulfamate ion from the *Sample solution*

USP Monographs

r_S = peak response of the sulfamate ion from the *Standard solution*
C_S = concentration of sulfamic acid in the *Standard solution* (mg/mL)
C_U = concentration of Topiramate in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of sulfamate anion, 96.09
M_{r2} = molecular weight of sulfamic acid, 97.09
Acceptance criteria: NMT 0.1% of sulfate; NMT 0.1% of sulfamate

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **LABELING:** If an *Organic Impurities* procedure other than *Procedure 2* is used, then the labeling states the test with which the article complies. The label also states that it is a suspected teratogen.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Fructose RS
  USP Topiramate RS
  USP Topiramate Related Compound A RS
  2,3:4,5-Bis-*O*-(1-methylethylidene)-*β*-D-fructopyranose.
  $C_{12}H_{20}O_6$ 260.28

Topiramate Capsules

DEFINITION
Topiramate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$).

IDENTIFICATION
- **A. INFRARED ABSORPTION** ⟨**197F**⟩
  Wavenumber range: 4000 to 650 cm^{-1}
  Standard solution: 20 mg/mL of USP Topiramate RS in acetone
  Sample solution: Open an appropriate number of Capsules to prepare a 20-mg/mL topiramate solution in acetone. Shake the solution for 30 min, and centrifuge for 10 min. Then pass an aliquot of the clear supernatant through a suitable nylon filter of 0.2-µm pore size, and use the filtrate for analysis.
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Apply 50 µL to an NaCl plate, allow the solution to dry, then obtain the IR spectrum.
  Acceptance criteria: Meet the requirements
- **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: 1.5 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.
  Diluent: Acetonitrile and water (20:80)
  Mobile phase: Methanol and *Buffer* (20:80)
  Standard solution: 6 mg/mL of USP Topiramate RS in *Diluent*
  Sample solution: Nominally 6 mg/mL of topiramate in *Diluent* from NLT 20 Capsules. [NOTE—Shake vigorously for at least 60 min, and pass a portion through a PTFE chemical-resistant filter of 0.45-µm pore size.]
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: Refractive index
  Column: 4.6-mm × 25-cm; 5-µm packing L1
  Flow rate: 1.5 mL/min
  Injection volume: 100 µL
  Temperatures
  Column: 35°
  Detector: 35°
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$) in the portion of Capsules 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 Topiramate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of topiramate in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
- **DISSOLUTION** ⟨**711**⟩
  Test 1
  Medium: Water; 900 mL
  Apparatus 2: 50 rpm. Use an appropriate sinker as necessary.
  Time: 45 min
  Standard stock solution: 0.56 mg/mL of USP Topiramate RS in *Medium* prepared as follows. Transfer a suitable amount to a suitable volumetric flask. Add 2% of the flask volume of acetone to dissolve the solid. Dilute with *Medium* to volume.
  Standard solution: (*L*/900) mg/mL of USP Topiramate RS in *Medium*, where *L* is the label claim, in mg of topiramate per Capsule from the *Standard stock solution*
  Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.
  Mobile phase: Methanol and water (32:68)
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: Refractive index
  Column: 4.6-mm × 15-cm; 5-µm packing L7
  Flow rate: 2 mL/min
  Injection volume: 200 µL
  Temperatures
  Column: 35°
  Detector: 35°
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Relative standard deviation: NMT 2.0% for Capsules labeled to contain more than 15 mg of topiramate; NMT 3.0% for Capsules labeled to contain less than or equal to 15 mg of topiramate
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*