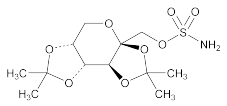
Topiramate



$C_{12}H_{21}NO_8S$ 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 topiramate ($C_{12}H_{21}NO_8S$), 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

Change to read:

- **PROCEDURE**

Mobile phase: Acetonitrile and water •(50:50)• (IRA 1-May-2017)
Standard solution: 2 mg/mL of USP Topiramate RS in *Mobile phase*
Sample solution: 2 mg/mL of Topiramate in *Mobile phase*
•**System suitability solution:** 0.02 mg/mL each of USP Fructose RS and USP Topiramate Related Compound A RS in the *Sample solution*• (IRA 1-May-2017)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Column: 50°
Detector: •55°• (IRA 1-May-2017)
Flow rate: 0.6 mL/min
Injection volume: 20 µL
•**Run time:** NLT 3 times the retention time of topiramate• (IRA 1-May-2017)
System suitability
Samples: *Standard solution* •and *System suitability solution*
[NOTE—See *Table 1* for the relative retention times for fructose, topiramate related compound A, and topiramate.]• (IRA 1-May-2017)
Suitability requirements
•**Resolution:** NLT 1.5 between topiramate related compound A and topiramate, *System suitability solution*• (IRA 1-May-2017)
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) 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

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

Change to read:

- **LIMIT OF SULFAMATE AND SULFATE**

[NOTE—Use water with resistivity of NLT 18 megohm-cm for preparation of the *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: •0.0045 mg/mL• (IRA 1-May-2017) of sodium sulfate and •0.0030 mg/mL• (IRA 1-May-2017) of sulfamic acid in *Mobile phase* •• (IRA 1-May-2017)
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 volume: 70 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention time of sulfamate is 0.44 relative to sulfate.]
Suitability requirements
Relative standard deviation: NMT 15.0% for sulfamate and sulfate
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 the sulfate ion from the *Sample solution*
r_S = peak response of the 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*
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

Delete the following:

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

Change to read:

[NOTE—•If *N*-methyltopiramate is a potential impurity, *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 3* are recommended; on the basis of synthetic route, perform either *Organic Impurities, Procedure 2* or *Organic Impurities, Procedure 3*.• (IRA 1-May-2017)]

Change to read:

- **ORGANIC IMPURITIES, 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⟩*, General Procedures, 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 •TS• (IRA 1-May-2017) (35:15:50)
Spray reagent: 30-mg/mL solution of phenol in alcohol and concentrated sulfuric 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 3*.• (IRA 1-May-2017)] 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 each *Standard solution*.
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 and NMT 0.5% of total impurities is found by TLC.

Change to read:

- **ORGANIC IMPURITIES, PROCEDURE 2**

Mobile phase: Prepare 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*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Column: •50°• (IRA 1-May-2017)
Detector: 55°
Flow rate: 0.6 mL/min
Injection volume: 50 µL
Run time: NLT 5 times the retention time of topiramate
System suitability
Sample: *System suitability solution*
[NOTE—•See *Table 1* for the relative retention times for fructose, topiramate related compound A, and topiramate.• (IRA 1-May-2017)]
Suitability requirements
Resolution: NLT 1.0 between topiramate related compound A and topiramate
Relative standard deviation: NMT 2.0% for topiramate
Analysis
Sample: *Sample solution*
Calculate the percentage of each •impurity• (IRA 1-May-2017) in the portion of Topiramate taken:

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

r_U = peak area of •each• (IRA 1-May-2017) impurity
r_T = sum of the peak areas of all the impurities and topiramate
F = relative response factor •(see *Table 1*)• (IRA 1-May-2017)

Acceptance criteria: See •• (IRA 1-May-2017)*Table 1*.

•**Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fructose	0.45	1.3	0.3
Topiramate related compound A	0.9	1.0	0.3
Topiramate	1.0	1.0	—
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.5

• (IRA 1-May-2017)

Change to read:

- **ORGANIC IMPURITIES, PROCEDURE 3**
  Mobile phase: Methanol and water •(32:68)• (IRA 1-May-2017)
  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 volume: 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 topiramate from six replicate injections
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of each •impurity• (IRA 1-May-2017) 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 •each• (IRA 1-May-2017) 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 •(see *Table 2*)• (IRA 1-May-2017)

  Acceptance criteria: •See *Table 2*.

Table 2

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Topiramate related compound A	1.1	0.3
Any individual unspecified impurity	1.0	0.10
Total impurities	1.0	0.5

• (IRA 1-May-2017)

SPECIFIC TESTS

- **OPTICAL ROTATION** ⟨**781S**⟩**,** *Procedures, Specific Rotation*
  Sample solution: 4–10 mg/mL in methanol
  Acceptance criteria: –28.6° to –35.0°, measured at 20°
- **WATER DETERMINATION** ⟨**921**⟩**,** *Method I***:** NMT 0.5%

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