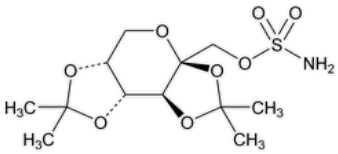
Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-B3F75255-1E8E-4BCC-B10C-DACD3DB504A5_4_en-US
DOI: https://doi.org/10.31003/USPNF_M84310_04_01
DOI Ref: 94q1f

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 CAS RN®: 97240-79-4; UNII: 0H73WJJ391.

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

Change to read:

• **A.** ▲**SPECTROSCOPIC IDENTIFICATION TESTS ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-MAY-2020)

• **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 (50:50)

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*

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°

Flow rate: 0.6 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of topiramate

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.]

Suitability requirements

Resolution: NLT 1.5 between topiramate related compound A and topiramate, *System suitability solution*

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%

• **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 of sodium sulfate and 0.0030 mg/mL of sulfamic acid in *Mobile phase*

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

[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*.]

- **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 chlorideTS (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*.] 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.

- **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°

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.]

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 in the portion of Topiramate taken:

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

r_U = peak area of each impurity

r_T = sum of the peak areas of all the impurities and topiramate

F = relative response factor (see *Table 1*)

Acceptance criteria: See *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

- **Organic Impurities, Procedure 3**

Mobile phase: Methanol and water(32:68)

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 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 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*)

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

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

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

Topic/Question	Contact	Expert Committee
TOPIRAMATE	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(6)

Current DocID: GUID-B3F75255-1E8E-4BCC-B10C-DACD3DB504A5_4_en-US
DOI: https://doi.org/10.31003/USPNF_M84310_04_01
DOI ref: 94q1f