Topiramate Tablets

DEFINITION
Topiramate Tablets 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: 4000–650 cm^{-1}
Standard solution: 20 mg/mL of USP Topiramate RS in acetone
Sample solution: Grind an appropriate number of Tablets 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 0.45-µm pore size, and use the filtrate for analysis.
Analysis: Apply 50 µL of the *Standard solution* to a sodium chloride plate, allow the solution to dry, and then obtain the IR spectrum. Wash the window with acetone, and repeat the same procedure using the *Sample solution.*
• **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: 1.54 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.
Diluent: Methanol and water (1:4)
Mobile phase: Methanol and *Buffer* (1:4)
Standard solution: 6 mg/mL of USP Topiramate RS in *Diluent*
Sample solution: 6 mg/mL of topiramate in *Diluent* from NLT 12 Tablets, based on the label claim. [NOTE—Shake vigorously for at least 30 min, and pass a portion through a chemical resistant 0.45-µm filter (PTFE).]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperature
Column: 35°
Detector: 35°
Flow rate: 1.5 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) in the portion of Tablets 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

Change to read:

• **Dissolution** ⟨711⟩
•**Test 1**• (RB 1-Oct-2010)
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 20 min
Standard solution: 0.1 mg/mL of USP Topiramate RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.
Mobile phase: 0.1% trifluoroacetic acid in water and methanol (1:1)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index
Guard column: 4.0-mm × 1-cm
Column: 4.6-mm × 25-cm; 5-µm packing L11
Temperature
Column: 40°
Detector: 40°
Flow rate: 1.2 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

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)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
Tolerances: NLT 80% (Q) of the labeled amount of topiramate is dissolved.
•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Water; 900 mL, deaerated
Apparatus 2: 50 rpm
Time: 40 min
Standard solution: (L/900) mg/mL of USP Topiramate RS in *Medium*, where L is the Tablet label claim in mg
Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few mL.
Mobile phase: Water and acetonitrile (1:1)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperature
Column: 30°
Detector: 50°
Flow rate: 1.0 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 5000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

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)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
Tolerances: NLT 80% (Q) of the labeled amount of topiramate is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Diluent: Acetonitrile and water (1:1)
Standard solution: 1.1 mg/mL of USP Topiramate RS in *Diluent*. Dilute with *Medium* to obtain a final concentration of about (L/900) mg/mL, where L is the Tablet label claim in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few mL.
Mobile phase: Water and acetonitrile (55:45)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperature
Column: 50°
Detector: 50°
Flow rate: 1.2 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 2000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

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)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
Tolerances: NLT 80% (Q) of the labeled amount of topiramate is dissolved. ●(RB 1-Oct-2010)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Related Compounds**
Diluent, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 1.2 mg/mL of USP Topiramate RS and 0.6 mg/mL of USP Topiramate Related Compound A RS in *Diluent*
Peak identification solution: 0.6 mg/mL each of USP Topiramate RS and USP Topiramate Related Compound A RS in *Diluent*
System suitability
Samples: *Standard solution* and *Peak identification solution*
[NOTE—Identify the peaks due to topiramate related compound A and topiramate using the relative retention times given in *Table 1*.]
Suitability requirements
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response for the individual impurity from the *Sample solution*
r_S = peak response of topiramate 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)
F = relative response factor (see *Table 1*)
Acceptance criteria
Individual impurities: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Topiramate related compound A	0.66	1.1	0.5
Topiramate	1.0	—	—
Individual unspecified degradation product	—	—	0.2
Total impurities	—	—	0.7

SPECIFIC TESTS

• **Limit of Sulfamate and Sulfate**
[NOTE—Use water with resistivity 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: 0.015 mg/mL each of sodium sulfate and sulfamic acid in *Mobile phase* from anhydrous sodium sulfate and sulfamic acid, respectively
Sample solution: Transfer a suitable amount of ground powder from NLT 20 Tablets to a suitable volumetric flask to

obtain a nominal concentration of 6 mg/mL of topiramate. Add 80% of the flask volume of *Mobile phase* and shake for 30 min. Sonicate for 10 min and dilute with *Mobile phase* to volume. Centrifuge and pass through a 0.45-µm polyethersulfone membrane filter, discarding the first 3 mL of the filtrate.

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—Suitable background suppression unit may be used.]
Injection size: 70 µL

System suitability
Sample: *Standard solution*
[NOTE—The approximate relative retention time of the sulfamate ion peak is 0.44 relative to the sulfate ion 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 ion in the portion of Tablets 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 sulfate anion, 96.04
M_{r2} = molecular weight of anhydrous sodium sulfate, 142.04

Calculate the percentage of sulfamate ion in the portion of Tablets taken:

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

r_U = peak response of sulfamate ion from the *Sample solution*
r_S = peak response of 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 0.25% of sulfate ion and NMT 0.25% of sulfamate ion

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store in tightly closed containers at controlled room temperature, protected from moisture.

Add the following:

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. (RB 1-Oct-2010)
- **USP REFERENCE STANDARDS** ⟨11⟩
USP Topiramate RS
2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate.
$C_{12}H_{21}NO_8S$ 339.36
USP Torsemide Related Compound A RS
4-[(3-Methylphenyl)amino]-3-pyridinesulfonamide.
$C_{12}H_{13}N_3O_2S$ 263.32