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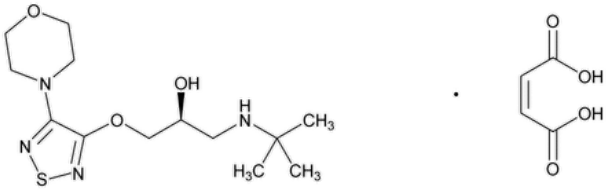
Timolol Maleate



$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ 432.49

2-Propanol, 1-[(1,1-dimethylethyl)amino]-3- [[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (*S*)-, (*Z*)-2-butenedioate (1:1) (salt);

(−)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt) CAS RN®: 26921-17-5; UNII: P8Y54F701R.

DEFINITION

Timolol Maleate contains NLT 98.0% and NMT 102.0% of timolol maleate ($C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M or 197A▲ (CN 1-May-2020)

• **B.** The retention time of the timolol peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the *Enantiomeric Purity* test.

ASSAY

• **Procedure**

Solution A: Dilute 0.5 mL of trifluoroacetic acid with water to 1 L.

Solution B: Dilute 0.5 mL of trifluoroacetic acid with acetonitrile to 1 L.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	84	16
2.4	84	16
8	20	80
8.1	84	16
11	84	16

Diluent: Methanol and water (60:40)

System suitability solution: 100 µg/mL of USP Timolol Maleate RS and 10 µg/mL of USP Timolol Related Compound D RS in *Diluent*

Standard solution: 100 µg/mL of USP Timolol Maleate RS in *Diluent*

Sample solution: 100 µg/mL of Timolol Maleate in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 295 nm

Column: 2.1-mm × 10-cm; 2.6-µm packing L1

Autosampler temperature: 4°

Flow rate: 0.4 mL/min

Injection volume: 2.5 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2 between timolol and timolol related compound D, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of timolol maleate ($C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$) in the portion of Timolol Maleate taken:

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

r_U = peak response of timolol from the *Sample solution*

r_S = peak response of timolol from the *Standard solution*

C_S = concentration of USP Timolol Maleate RS in the *Standard solution* (µg/mL)

C_U = concentration of Timolol Maleate in the *Sample solution* (µg/mL)

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Change to read:

• **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

▲Sensitivity solution: 0.5 µg/mL of USP Timolol Maleate RS in *Diluent*▲ (USP 1-Dec-2019)

System suitability solution: 100 µg/mL each of USP Timolol Maleate RS, USP Timolol Related Compound B RS, USP Timolol Related Compound C RS, USP Timolol Related Compound D RS, USP Timolol Related Compound E RS, and USP Timolol Related Compound F RS in *Diluent*. [Note—Prepare fresh and analyze immediately as USP Timolol Related Compound E RS degrades rapidly.]

Standard solution: 1 µg/mL of USP Timolol Maleate RS and 4 µg/mL each of USP Timolol Related Compound B RS, USP Timolol Related Compound C RS, USP Timolol Related Compound D RS, USP Timolol Related Compound E RS, and USP Timolol Related Compound F RS in *Diluent*. Sonicate if needed for 0.5 min.

Sample solution: 1 mg/mL of Timolol Maleate in *Diluent*

System suitability

Samples: ▲*Sensitivity solution*,▲ (USP 1-Dec-2019) *System suitability solution*, and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between timolol and timolol related compound D, *System suitability solution*

Relative standard deviation: NMT 4.0% for timolol, *Standard solution*

▲Signal-to-noise ratio: NLT 10 for timolol, *Sensitivity solution*▲ (USP 1-Dec-2019)

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of timolol maleate ester (free base of timolol related compound E) in the portion of Timolol Maleate taken:

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

r_U = peak response of timolol maleate ester from the *Sample solution*

r_S = peak response of timolol maleate ester from the *Standard solution*

C_S = concentration of USP Timolol Related Compound E RS in the *Standard solution* (µg/mL)

C_U = concentration of Timolol Maleate in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of timolol maleate ester, 414.48

M_{r2} = molecular weight of timolol related compound E, 530.55

Calculate the percentage of timolol bisthiadiazol analog (free base of timolol related compound C) in the portion of Timolol Maleate taken:

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

r_U = peak response of timolol bisthiadiazol from the *Sample solution*

r_S = peak response of timolol bisthiadiazol from the *Standard solution*

C_S = concentration of USP Timolol Related Compound C RS in the *Standard solution* (µg/mL)

C_U = concentration of Timolol Maleate in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of timolol bisthiadiazol, 485.62

M_{r2} = molecular weight of timolol related compound C, 601.69▲ (USP 1-Dec-2019)

Calculate the percentage of ▲timolol related compound B, D, or F▲ (USP 1-Dec-2019) in the portion of Timolol Maleate taken:

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

r_U = peak response of ▲timolol related compound B, D, or F▲ (USP 1-Dec-2019) from the *Sample solution*

r_S = peak response of ▲timolol related compound B, D, or F▲ (USP 1-Dec-2019) from the *Standard solution*

C_S = concentration of ▲USP Timolol Related Compound B RS, USP Timolol Related Compound D RS, or USP Timolol Related Compound F RS▲ (USP 1-Dec-2019) in the *Standard solution* (µg/mL)

C_U = concentration of Timolol Maleate in the *Sample solution* (µg/mL)

Calculate the percentage of any individual unspecified impurity in the portion of Timolol Maleate taken:

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

r_U = peak response of any individual unspecified impurity from the *Sample solution*

r_S = peak response of timolol from the *Standard solution*

C_S = concentration of USP Timolol Maleate RS in the *Standard solution* (µg/mL)

C_U = concentration of Timolol Maleate in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (USP 1-Dec-2019)

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Timolol related compound B	0.5	0.4
Timolol related compound D	0.8	0.4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Timolol maleate	1.0	—
▲Timolol maleate ester[a]▲ (USP 1-Dec-2019)	1.4	0.4
▲Timolol bisthiadiazol analog[b]▲ (USP 1-Dec-2019)	1.8	0.4
Timolol related compound F	2.0	0.4
Any individual unspecified impurity	—	0.10
▲Total impurities▲ (USP 1-Dec-2019)	—	1.0

▲[a] (*S*)-3-(*tert*-Butylamino)-1-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-yl hydrogen maleate.

[b] *N*-(*tert*-Butyl)-2,3-bis(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-1-amine.▲ (USP 1-Dec-2019)

Change to read:

• **Enantiomeric Purity**

Prepare all solutions in low-actinic glassware protected from light.

Mobile phase: Diethylamine, 2-propanol, and hexane (2:40:960)

Diluent: Methylene chloride and 2-propanol (25:75)

System suitability solution: 0.03 mg/mL each of USP Timolol Maleate RS and USP Timolol Related Compound A RS in *Diluent*

Standard solution: 0.03 mg/mL of USP Timolol Related Compound A RS in *Diluent*

Sample solution: 3 mg/mL of Timolol Maleate in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 297 nm

Column: 4.6-mm × 25-cm; 5-µm packing L40

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Samples: *System suitability solution* ▲and *Standard solution*▲ (USP 1-Dec-2019)

Suitability requirements

Resolution: NLT 4.0 between the timolol related compound A and timolol peaks, *System suitability solution*

Relative standard deviation: NMT 1.5% for ▲the timolol related compound A peak, *Standard solution*▲ (USP 1-Dec-2019)

Signal-to-noise ratio: NLT 10 for the timolol related compound A peak, ▲*Standard solution*▲ (USP 1-Dec-2019)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of timolol related compound A in the portion of Timolol Maleate taken:

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

r_U = peak response of timolol related compound A from the *Sample solution*

r_S = peak response of timolol related compound A from the *Standard solution*

C_S = concentration of USP Timolol Related Compound A RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 20 mg/mL of Timolol Maleate in water

Acceptance criteria: 3.8–4.3

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at 100° to constant weight.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in well-closed containers, ▲protected from light.▲ (USP 1-Dec-2019)

• **USP Reference Standards** ⟨11⟩

USP Timolol Maleate RS

USP Timolol Related Compound A RS

(*R*)-1-(*tert*-Butylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ 432.49

USP Timolol Related Compound B RS

3-(*tert*-Butylamino)-2-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-1-ol.

$C_{13}H_{24}N_4O_3S$ 316.42

USP Timolol Related Compound C RS

N-(*tert*-Butyl)-2,3-bis(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-1-amine maleate.

$C_{19}H_{31}N_7O_4S_2 \cdot C_4H_4O_4$ 601.69

USP Timolol Related Compound D RS

4-Morpholino-1,2,5-thiadiazol-3-ol.

$C_6H_9N_3O_2S$ 187.22

USP Timolol Related Compound E RS

(*S*, *Z*)-4-({1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]propan-2-yl}oxy)-4-oxobut-2-enoic acid maleate salt (1:1).

$C_{17}H_{26}N_4O_6S \cdot C_4H_4O_4$ 530.55

USP Timolol Related Compound F RS

3-Chloro-4-morpholino-1,2,5-thiadiazol.

$C_6H_8ClN_3OS$ 205.67

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

Topic/Question	Contact	Expert Committee
TIMOLOL MALEATE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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