Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Dec-2021
Document Type: USP Monographs
DocId: GUID-9F17C03C-3357-43B3-8E2B-E026F574B543_6_en-US
DOI: https://doi.org/10.31003/USPNF_M28042_06_01
DOI Ref: 9u0rj

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

DEFINITION

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution is a sterile, isotonic, buffered, slightly viscous, aqueous solution of Dorzolamide Hydrochloride and Timolol Maleate. It contains NLT 90.0% and NMT 110.0% of the labeled amount of dorzolamide ($C_{10}H_{16}N_2O_4S_3$) and NLT 90.0% and NMT 110.0% of the labeled amount of timolol ($C_{13}H_{24}N_4O_3S$). It may contain a suitable preservative.

IDENTIFICATION

Change to read:

• **A.** ▲The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*, *Procedure for Dorzolamide*.▲ (USP 1-Dec-2021)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*, *Procedure for Dorzolamide*.

• **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*, *Procedure for Timolol*.

Add the following:

▲• **D.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*, *Procedure for Timolol*.▲ (USP 1-Dec-2021)

ASSAY

Change to read:

• **Procedure for Dorzolamide**

Solution A: Acetonitrile

Solution B: 0.2% (v/v) phosphoric acid in water

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	5	95
15.0	5	95
15.1	95	5
20.0	95	5
20.1	5	95
30.0	5	95

Diluent: Acetonitrile and *Solution B* (5:95)

Standard solution: 0.11 mg/mL of USP Dorzolamide Hydrochloride RS and 0.5 µg/mL each of USP Dorzolamide Related Compound B RS and USP Dorzolamide Related Compound D RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of dorzolamide in *Diluent*, from Ophthalmic Solution

Chromatographic system

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

Mode: LC

Detector: UV 253 nm. ▲For *Identification A*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-Dec-2021)

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 3.0 between dorzolamide and dorzolamide related compound D; NLT 3.0 between dorzolamide and dorzolamide related compound B

Relative standard deviation: NMT 2.0% for dorzolamide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of dorzolamide ($C_{10}H_{16}N_2O_4S_3$) in the portion of Ophthalmic Solution taken:

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

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

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

C_S = concentration of USP Dorzolamide Hydrochloride RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of dorzolamide, ▲324.43▲ (USP 1-Dec-2021)

M_{r2} = molecular weight of dorzolamide hydrochloride, ▲360.89▲ (USP 1-Dec-2021)

Acceptance criteria: 90.0%–110.0%

Change to read:

• **PROCEDURE FOR TIMOLOL**

Buffer: Transfer 22 g of sodium phosphate, monobasic into a 2000-mL volumetric flask. Dissolve in 1995 mL of water, and adjust with phosphoric acid to a pH of 2.8. Dilute with water to volume.

Mobile phase: Methanol and *Buffer* (40:60)

System suitability solution: Transfer 88 mg of USP Timolol Maleate RS into a 50-mL volumetric flask. Transfer 8 mL of 0.1 M sodium hydroxide into the flask, mix, and heat at 70° for 15 h. Dilute with *Mobile phase* to volume, and mix well. Transfer 5 mL of this solution into a 25-mL volumetric flask, and add 28 mg of USP Dorzolamide Hydrochloride RS into the same flask. Dilute with *Mobile phase* to volume. [NOTE—The preparation generates timolol impurity G and timolol related compound B.]

Standard solution: 0.35 mg/mL of USP Timolol Maleate RS in *Mobile phase*

Sample solution: Nominally 0.25 mg/mL of timolol in *Mobile phase*, from Ophthalmic Solution

Chromatographic system

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

Mode: LC

Detector: UV 295 nm. ▲For *Identification D*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-Dec-2021)

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between timolol impurity G and timolol related compound B

Relative standard deviation: NMT 2.5% for timolol for 5 replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of timolol ($C_{13}H_{24}N_4O_3S$) in the portion of Ophthalmic Solution 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 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* (mg/mL)

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

M_{r1} = molecular weight of timolol, 316.42

M_{r2} = molecular weight of timolol maleate, 432.49

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

• **Organic Impurities, Dorzolamide Hydrochloride**

▲Solution A, Solution B,▲ (USP 1-Dec-2021) Mobile phase, ▲ Diluent,▲ (USP 1-Dec-2021) Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*, *Procedure for Dorzolamide*.

▲System suitability solution: Use the *Standard solution* as prepared in the *Assay*, *Procedure for Dorzolamide*.

Standard solution: 0.5 µg/mL each of USP Dorzolamide Related Compound B RS and USP Dorzolamide Related Compound D RS in *Diluent*▲ (USP 1-Dec-2021)

System suitability

Sample: ▲*System suitability solution*▲ (USP 1-Dec-2021)

Suitability requirements

Resolution: NLT 3.0 between dorzolamide and dorzolamide related compound D; NLT 3.0 between dorzolamide and dorzolamide related compound B

Relative standard deviation: NMT 2.0% for dorzolamide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dorzolamide related compound D in the portion of Ophthalmic Solution taken:

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

r_U = peak area of dorzolamide related compound D from the *Sample solution*

r_S = peak area of dorzolamide related compound D from the *Standard solution*

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

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

M_{r1} = molecular weight of dorzolamide, ▲324.43▲ (USP 1-Dec-2021)

M_{r2} = molecular weight of dorzolamide related compound D, ▲332.83▲ (USP 1-Dec-2021)

Calculate the percentage of dorzolamide related compound B in the portion of Ophthalmic Solution taken:

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

r_U = peak area of dorzolamide related compound B from the *Sample solution*

r_S = peak area of dorzolamide related compound B from the *Standard solution*

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

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

M_{r1} = molecular weight of dorzolamide, ▲324.43▲ (USP 1-Dec-2021)

M_{r2} = molecular weight of dorzolamide related compound B, ▲360.89▲ (USP 1-Dec-2021)

Calculate the percentage of each individual unspecified impurity in the portion of Ophthalmic Solution taken:

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

r_U = peak area of each individual unspecified impurity from the *Sample solution*

r_T = sum of all the peak areas from the *Sample solution*

Acceptance criteria: See *Table 2*. The reporting threshold is 0.10%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Maleic acid	0.33	Disregard
Dorzolamide related compound D	0.83	0.5
Dorzolamide	1.00	—
Dorzolamide related compound B	1.17	2.0
Any individual unspecified impurity	—	0.5
Total impurities[a]	—	3.0

[a] It is the sum of all impurities in *Table 2* and dorzolamide maleic acid adducts in *Table 5*.

Change to read:

• **Organic Impurities, Timolol Maleate**

▲**Buffer,**▲ (USP 1-Dec-2021) **Mobile phase, System suitability solution,** and **Sample solution:** Prepare as directed in the *Assay*, *Procedure for Timolol*.

Standard stock solution: Use the *Standard solution* as prepared in the *Assay*, *Procedure for Timolol*.

Standard solution: 3.5 µg/mL of USP Timolol Maleate RS in *Mobile phase*, from the *Standard stock solution*

Chromatographic system: Proceed as directed in the *Assay*, *Procedure for Timolol* except for the *Run time*.

Run time: NLT 2 times the retention time of timolol

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between timolol impurity G and timolol related compound B

Relative standard deviation: NMT 2.5% for timolol for 5 replicate injections

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each individual impurity in the portion of Ophthalmic Solution taken:

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

r_U = peak area of each individual impurity from the *Sample solution*

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

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

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

M_{r1} = molecular weight of timolol, 316.42

M_{r2} = molecular weight of timolol maleate, 432.49

Acceptance criteria: See *Table 3*. The reporting threshold is 0.10%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Dorzolamide and maleic acid	0.49	Disregard
Timolol impurity G[a]	0.58	0.5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Timolol related compound B[b]	0.70	1.0
Timolol	1.00	—
Timolol related compound D[c]	1.51	0.5
Any individual unspecified impurity	—	0.6
Total impurities	—	2.0

[a] 4-Morpholino-1,2,5-thiadiazol-3-ol 1-oxide.

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

[c] 4-Morpholino-1,2,5-thiadiazol-3-ol.

Change to read:

• **Limit of Dorzolamide Maleic Acid Adducts**

Solution A, Solution B, ▲Diluent,▲ (USP 1-Dec-2021) **Standard solution, Sample solution, Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*, *Procedure for Dorzolamide*.

Mobile phase: See *Table 4*. Return to original conditions and re-equilibrate the system for 6 min.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	5	95
15.0	5	95
15.1	13	87
20.0	13	87
25.0	95	5
29.0	95	5

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dorzolamide maleic acid adduct in the portion of Ophthalmic Solution taken:

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

r_U = peak area of dorzolamide maleic acid adduct from the *Sample solution*

r_S = peak area of dorzolamide from the *Standard solution*

C_S = concentration of USP Dorzolamide Hydrochloride RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of dorzolamide, ▲324.43▲ (USP 1-Dec-2021)

M_{r2} = molecular weight of dorzolamide hydrochloride, ▲360.89▲ (USP 1-Dec-2021)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Dorzolamide	1.00	—
Dorzolamide maleic acid adducts[a,b]	1.71	0.5
	1.78	0.5

[a] The chromatographic system resolves the two epimers from each other.

[b] *N*-Ethyl-*N*-[(4*S*,6*S*)-6-methyl-7,7-dioxido-2-sulfamoyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-yl]aspartic acid.

SPECIFIC TESTS

• **Sterility Tests ⟨71⟩:** Meets the requirements

• **pH ⟨791⟩:** 5.4–5.9 at 22°

Add the following:

▲• **Other Requirements:** It meets the requirements in *Ophthalmic Products—Quality Tests ⟨771⟩*.▲ (USP 1-Dec-2021)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers protected from light, at controlled room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Dorzolamide Hydrochloride RS

USP Dorzolamide Related Compound B RS

(4*RS*,6*SR*)-4-(Ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

$C_{10}H_{16}N_2O_4S_3 \cdot HCl$ ▲360.89▲ (USP 1-Dec-2021)

USP Dorzolamide Related Compound D RS

(4*S*,6*S*)-4-Amino-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

$C_8H_{12}N_2O_4S_3 \cdot HCl$ ▲332.83▲ (USP 1-Dec-2021)

USP Timolol Maleate RS

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

Topic/Question	Contact	Expert Committee
DORZOLAMIDE HYDROCHLORIDE AND TIMOLOL MALEATE OPHTHALMIC SOLUTION	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(4)

Current DocID: GUID-9F17C03C-3357-43B3-8E2B-E026F574B543_6_en-US

DOI: https://doi.org/10.31003/USPNF_M28042_06_01

DOI ref: 9u0rj