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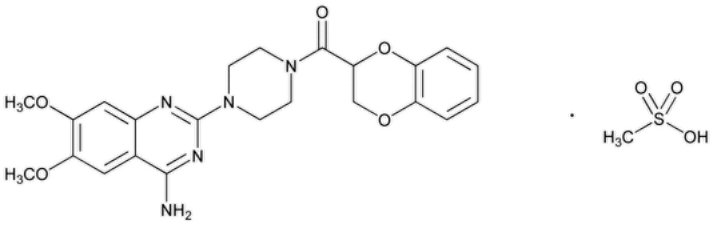
Doxazosin Mesylate



$C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ 547.58

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate;

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine monomethanesulfonate CAS RN®: 77883-43-3; UNII: 86P6PQK0MU.

DEFINITION

Doxazosin Mesylate contains NLT 98.0% and NMT 102.0% of doxazosin mesylate ($C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$), calculated on the dried basis.

IDENTIFICATION

- **A.** **Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **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

- **Procedure**

Solution A: 50 mg/mL (w/v) of phosphoric acid in water

Solution B: Acetonitrile

Solution C: Water

Solution D: Mix 100 mL of *Solution B* and 2 g of phosphoric acid.

Mobile phase: See *Table 1*.

Table 1[a]

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	20	10	70
10	20	22	58
35	20	50	30
40	20	50	30

[a] Between sample injections, the system is re-equilibrated for at least 7 min or until a stable baseline is obtained, representing the starting composition.

System suitability solution: 12 µg/mL of USP Doxazosin Related Compound A RS and 12 µg/mL of USP Doxazosin Related Compound B RS in a mixture of *Solution C* and *Solution D* (9:1). Initially add about 2.5 mL of *Solution D* and then add *Solution D* or *Solution C* to maintain a final composition of *Solution C* and *Solution D* in the ratio of 9:1. Sonicate briefly for complete dissolution.

Standard solution: 0.6 mg/mL of USP Doxazosin Mesylate RS in a mixture of *Solution C* and *Solution D* (9:1). Initially add about 2 mL of *Solution D* and then add *Solution D* or *Solution C* to maintain a final composition of *Solution C* and *Solution D* in the ratio of 9:1. Sonicate briefly for complete dissolution.

Sample solution: 0.6 mg/mL of Doxazosin Mesylate in a mixture of *Solution C* and *Solution D* (9:1). Initially add about 2 mL of *Solution D* and then add *Solution D* or *Solution C* to maintain a final composition of *Solution C* and *Solution D* in the ratio of 9:1. Sonicate briefly for complete dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4-mm × 25-cm; 5-µm packing L7

Column temperature: 35°

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 2 between doxazosin related compound A and doxazosin related compound B, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of doxazosin mesylate ($C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$) in the portion of Doxazosin Mesylate 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 Doxazosin Mesylate RS in the *Standard solution* (mg/mL)

C_U = concentration of Doxazosin Mesylate in the *Sample solution* (mg/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, Solution C, Solution D, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.0015 mg/mL each of USP Doxazosin Mesylate RS, USP Doxazosin Related Compound A RS, USP Doxazosin Related Compound B RS, USP Doxazosin Related Compound C RS, USP Doxazosin Related Compound D RS, USP Doxazosin Related Compound E RS, USP Doxazosin Related Compound F RS, USP Terazosin Related Compound A RS, and USP Terazosin Related Compound C RS in a mixture of *Solution C* and *Solution D*. Initially dissolve USP Doxazosin Related Compounds A, B, C, D, E, and F RS and USP Terazosin Related Compounds A and C RS in approximately 2 mL of *Solution D* only and then add *Solution D* or *Solution C* to maintain a final composition of *Solution C* and *Solution D* in the ratio of 9:1. Sonicate briefly for complete dissolution.

Sample solution: 0.6 mg/mL of Doxazosin Mesylate in a mixture of *Solution C* and *Solution D* (9:1). Initially add about 2 mL of *Solution D* and then add *Solution D* or *Solution C* to maintain a final composition of *Solution C* and *Solution D* in the ratio of 9:1. Sonicate briefly for complete dissolution.

System suitability

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

Suitability requirements

Resolution: NLT 2 between doxazosin related compound A and doxazosin related compound B, *System suitability solution*

Relative standard deviation: NMT 10% for all peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Doxazosin Mesylate taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of each impurity or doxazosin mesylate (for calculating unspecified impurities) from the *Standard solution*

C_S = concentration of the corresponding ▲USP Reference Standard▲ (ERR 1-Nov-2022) or USP Doxazosin Mesylate RS (for calculating unspecified impurities) in the *Standard solution* (mg/mL)

C_U = concentration of Doxazosin Mesylate in the *Sample solution* (mg/mL)

M_{r2} = molecular weight of the corresponding impurity in the sample (see *Table 2*)

M_{r1} = molecular weight of corresponding impurity Reference Standard (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Molecular Weight of Reference Standard (M_{r1})	Molecular Weight of Corresponding Impurity in Sample (M_{r2})	Acceptance Criteria, NMT (%)
Terazosin related compound A[a,b]	0.20	362.25	481.55	0.3
Doxazosin related compound A[c,b]	0.44	248.28	344.39	0.25
Doxazosin related compound B[d]	0.48	222.20	222.20	0.25
Doxazosin related compound C[e,b]	0.56	239.66	335.77	0.25
Terazosin related compound C[f,b]	0.61	565.45	684.75	0.25
Doxazosin related compound D[g]	0.83	180.16	180.16	0.25
Doxazosin mesylate	1.00	—	—	—
Doxazosin related compound E[h]	1.45	259.09	259.09	0.25
Doxazosin related compound F[i]	1.55	410.42	410.42	0.25
Any unspecified impurity	—	—	—	0.10
Total impurities	—	—	—	1.0

[a] 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.

[b] This impurity exists as a mesylate salt in the sample.

[c] *N*-1,4-Benzodioxane-2-carbonyl piperazine.

[d] 6,7-Dimethoxyquinazoline-2,4-dione.

[e] 2-Chloro-4-amino-6,7-dimethoxy quinazoline.

[f] 1,4-Bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.

[g] 1,4-Benzodioxane-2-carboxylic acid.

[h] 2,4-Dichloro-6,7-dimethoxyquinazoline.

[i] *N,N'*-Bis(1,4-benzodioxane-2-carbonyl)piperazine.

SPECIFIC TESTS

• **Loss on Drying (731)**

Sample: 1.0 g

Analysis: Dry the *Sample* under vacuum at 105° for 4 h.

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store below 30°.

• **USP Reference Standards (11)**

USP Doxazosin Mesylate RS

USP Doxazosin Related Compound A RS

N-1,4-Benzodioxane-2-carbonyl piperazine.

$C_{13}H_{16}N_2O_3$ 248.28

USP Doxazosin Related Compound B RS

6,7-Dimethoxyquinazoline-2,4-dione.

$C_{10}H_{10}N_2O_4$ 222.20

USP Doxazosin Related Compound C RS

2-Chloro-4-amino-6,7-dimethoxyquinazoline.

$C_{10}H_{10}ClN_3O_2$ 239.66

USP Doxazosin Related Compound D RS

1,4-Benzodioxane-2-carboxylic acid.

$C_9H_8O_4$ 180.16

USP Doxazosin Related Compound E RS

2,4-Dichloro-6,7-dimethoxyquinazoline.

$C_{10}H_8Cl_2N_2O_2$ 259.09

USP Doxazosin Related Compound F RS

N,N'-Bis(1,4-benzodioxane-2-carbonyl)piperazine.

$C_{22}H_{22}N_2O_6$ 410.42

USP Terazosin Related Compound A RS

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.

$C_{14}H_{19}N_5O_2 \cdot 2HCl$ 362.25

USP Terazosin Related Compound C RS

1,4-Bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride.

$C_{24}H_{28}N_8O_4 \cdot 2HCl$ 565.45

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

Topic/Question	Contact	Expert Committee
DOXAZOSIN MESYLATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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