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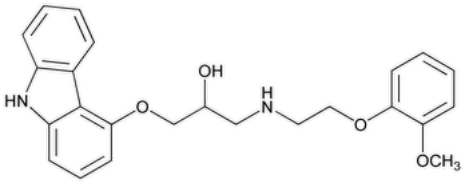
Carvedilol



$C_{24}H_{26}N_2O_4$ 406.47

2-Propanol, 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2- methoxyphenoxy)ethyl]amino]-, (±)-;

(±)-1-(Carbazol-4-yloxy)-3-[[2-(*o*-methoxyphenoxy)eth yl]amino]-2-propanol CAS RN®: 72956-09-3; UNII: 0K47UL67F2.

DEFINITION

Carvedilol contains NLT 98.0% and NMT 102.0% of $C_{24}H_{26}N_2O_4$, 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**

Buffer: 2.72 g/L of monobasic potassium phosphate. Adjust with dilute phosphoric acid to a pH of 2.0.

Mobile phase: Acetonitrile and *Buffer* (31:69)

System suitability solution: 0.05 mg/mL each of USP Carvedilol RS and USP Carvedilol Related Compound A RS in *Mobile phase*

Standard solution: 0.04 mg/mL of USP Carvedilol RS in *Mobile phase*

Sample solution: 0.04 mg/mL of Carvedilol in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 55°

Flow rate: 1 mL/min

Run time: 60 min

Injection size: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 4.0 between carvedilol and carvedilol related compound A

Tailing factor: NMT 1.5 for the carvedilol peak

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of carvedilol ($C_{24}H_{26}N_2O_4$) in the portion of the sample taken:

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

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

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

C_S = concentration of carvedilol in the *Standard solution* (mg/mL)

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1% from 1 g

• **Organic Impurities, Procedure 1:** [Note—On the basis of the impurities present, perform either *Organic Impurities, Procedure 1* or *Organic Impurities, Procedure 2*. *Organic Impurities, Procedure 2* is recommended when carvedilol related compound F is a potential impurity.]

Buffer and **Mobile phase:** Prepare as directed in the *Assay*.

System suitability solution: 0.05 mg/mL each of USP Carvedilol RS and USP Carvedilol Related Compound C RS in *Mobile phase*

Standard solution: 1 µg/mL each of USP Carvedilol RS, USP Carvedilol Related Compound A RS, USP Carvedilol Related Compound B RS, USP Carvedilol Related Compound D RS, and USP Carvedilol Related Compound E RS, and 0.2 µg/mL of USP Carvedilol Related Compound C RS in *Mobile phase*

Sample solution: 1 mg/mL of Carvedilol in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: Dual wavelength, UV 220 and 240 nm. Use 220 nm for quantitating carvedilol related compound E, and use 240 nm for carvedilol and all other related compounds.

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 55°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 17 between carvedilol and carvedilol related compound C

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of carvedilol related compound A, carvedilol related compound B, carvedilol related compound C, carvedilol related compound D, carvedilol related compound E, and any other individual impurity in the portion of Carvedilol taken:

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

r_U = peak response of the corresponding related compound or any other impurity from the *Sample solution*

r_S = peak response of the corresponding related compound from the *Standard solution*. To calculate the percentage of any other individual impurity use the peak response of carvedilol.

C_S = concentration of the corresponding related compound in the *Standard solution* (mg/mL). To calculate the percentage of any other impurities for C_S, use the concentration of USP Carvedilol RS.

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Carvedilol related compound E[a]	0.35	0.1
Carvedilol related compound A[b]	0.52	0.1
Carvedilol bisalkylpyrocatechol derivative (if present)[c]	0.70	0.15
Carvedilol	1.0	—
Carvedilol related compound C[d]	3.6	0.02

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Carvedilol related compound D[e]	5.0	0.1
Carvedilol related compound B[f]	8.5	0.1
Any other individual impurity	—	0.10
Total impurities	—	0.5[g]

[a] 2-(2-Methoxyphenoxy)ethyl amine.

[b] 1-(4-(2-Hydroxy-3-(2-(2-methoxyphenoxy)ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol.

[c] 3,3'-{2,2'-[1,2-Phenylenebis(oxy)]bis(ethane-2,1-diyl)}bis(azanediyl)bis(1-(9*H*-carbazol-4-yloxy)propan-2-ol).

[d] 1-(9*H*-Carbazol-4-yloxy)-3-(benzyl(2-(2-methoxyphenoxy)ethyl) amino)propan-2-ol.

[e] 4-(Oxiran-2-ylmethoxy)-9*H*-carbazole.

[f] 3,3'-(2-(2-Methoxyphenoxy)ethylazanediyl)bis(1-(9*H*-carbazol-4-yl oxy)propan-2-ol).

[g] Disregard any impurity less than 0.01%.

Change to read:

• **Organic Impurities, Procedure 2**

Solution A: Acetonitrile and trifluoroacetic acid (100:0.1)

Solution B: Trifluoroacetic acid and water (0.1:100)

Diluent: Acetonitrile, trifluoroacetic acid, and water (22:0.1:78)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	22	78
20	22	78
33	38	62
45	38	62
55	55	45
65	55	45
68	22	78
80	22	78

System suitability solution: 1.0 mg/mL of USP Carvedilol System Suitability Mixture RS in *Diluent*

Sample solution: 1 mg/mL of Carvedilol in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 5-µm packing L68

Column temperature: 30°

Flow rate: 1.4 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.8 between carvedilol and carvedilol related compound F

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Carvedilol taken:

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

r_U = peak response for each impurity in the *Sample solution*

r_T = sum of all the peak responses in the *Sample solution*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Carvedilol related compound A[a]	0.7	0.1
Carvedilol	1.0	—
Carvedilol related compound F[b]	1.2	0.1[c]
N-Isopropylcarvedilol[d]	1.6	0.1
Carvedilol related compound C[e]	1.8	0.02
Carvedilol related compound B[f]	2.1	0.1
Biscarbazole[g]	3	0.1
Any other individual impurity	—	0.1
Total impurities	—	0.5

[a] 1-(4-(2-Hydroxy-3-(2-(2-methoxyphenoxy)ethylamino)propoxy)-9*H*carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol.

▲[b] 1-(2-(2-Methoxyphenoxy)ethylamino)-3-(2,3,4,9-tetrahydro-1*H*-carbazol-5-yloxy)propan-2-ol.▲ (ERR 1-Jan-2021)

[c] This impurity is quantitated using the procedure under *Organic Impurities, Procedure 3: Carvedilol Related Compound F*.

[d] 1-(*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]*N*-isopropylamino]-2-propanol.

[e] 1-(9*H*-Carbazol-4-yloxy)-3-(benzyl(2-(2-methoxyphenoxy)ethyl)amino) propan-2-ol.

[f] 3,3'-(2-(2-Methoxyphenoxy)ethylazanediyl)bis(1-(9*H*-carbazol-4-yl oxy)propan-2-ol).

[g] 1,3-Bis-(9*H*-carbazol-4-yloxy)-2-propanol.

• **Organic Impurities, Procedure 3: Carvedilol Related Compound F** (if present)

Solution A: Trifluoroacetic acid and water (0.5:100)

Solution B: Methanol and trifluoroacetic acid (100:0.5)

Diluent: Water and acetonitrile (1:1)

Mobile phase: *Solution A* and *Solution B* (65:35)

System suitability solution: 1.5 mg/mL of USP Carvedilol System Suitability Mixture RS in *Diluent*

Sample solution: 1.5 mg/mL of Carvedilol in *Diluent* prepared as follows. Initially add *Diluent* to fill about 80% of the total volume. Sonicate briefly to facilitate dissolution. Cool, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 30-mm; 3-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection size: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between carvedilol and carvedilol related compound F

Analysis

Sample: *Sample solution*

Calculate the percentage of carvedilol related compound F in the portion of the sample taken:

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

r_U = peak response of carvedilol related compound F from the *Sample solution*

r_T = sum of the peak responses of carvedilol and carvedilol related compound F from the *Sample solution*

F = relative response factor, 1.1

Acceptance criteria: NMT 0.1%

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩:** Dry a sample at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

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

• **Labeling:** If a test for *Organic Impurities* by HPLC other than *Procedure 1* is used, then the labeling states the test with which the article complies.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Carvedilol RS

USP Carvedilol Related Compound A RS

1-(4-(2-Hydroxy-3-(2-(2-methoxy phenoxy)ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol.

$C_{36}H_{43}N_3O_7$ ▲629.75▲ (ERR 1-Jan-2021)

USP Carvedilol Related Compound B RS

3,3'-(2-(2-Methoxyphenoxy)ethylazanediyl)bis(1-(9*H*-carbazol-4-yloxy)propan-2-ol).

$C_{39}H_{39}N_3O_6$ ▲645.76▲ (ERR 1-Jan-2021)

USP Carvedilol Related Compound C RS

1-(9*H*-Carbazol-4-yloxy)-3-(benzyl(2-(2-methoxyphen oxy)ethyl)amino)propan-2-ol.

$C_{31}H_{32}N_2O_4$ ▲496.61▲ (ERR 1-Jan-2021)

USP Carvedilol Related Compound D RS

4-(Oxiran-2-ylmethoxy)-9*H*-carbazole.

$C_{15}H_{13}NO_2$ 239.27

USP Carvedilol Related Compound E RS

▲[Note—This material may be available in the free base or salt form.]▲ (ERR 1-Jan-2021)

2-(2-Methoxyphenoxy)ethyl amine.

$C_9H_{13}NO_2$ 167.21

▲2-(2-Methoxyphenoxy)ethyl amine hydrochloride monohydrate.

$C_9H_{13}NO_2 \cdot HCl \cdot H_2O$ 221.68▲ (ERR 1-Jan-2021)

USP Carvedilol System Suitability Mixture RS

▲Contains a mixture of carvedilol related compound F in a matrix of carvedilol drug substance:

Carvedilol.

Carvedilol related compound F.

[Note—This material may be available in the free base or salt form.]

1-(2-(2-Methoxyphenoxy)ethylamino)-3-(2,3,4,9-tetrahydro-1*H*-carbazol-5-yloxy)propan-2-ol.

$C_{24}H_{30}N_2O_4$ 410.51

1-(2-(2-Methoxyphenoxy)ethylamino)-3-(2,3,4,9-tetrahydro-1*H*-carbazol-5-yloxy)propan-2-ol acetate.

$C_{24}H_{30}N_2O_4 \cdot C_2H_4O_2$ 470.57▲ (ERR 1-Jan-2021)

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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