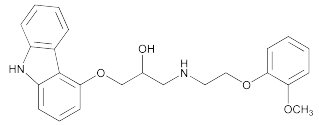
Carvedilol



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

2-Propanol, 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (±)-;
(±)-1-(Carbazol-4-yloxy)-3-[[2-(*o*-methoxyphenoxy)ethyl]amino]-2-propanol [72956-09-3].

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. Infrared Absorption** ⟨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 Car vedilol Related Compound A RS in *Mobile phase*
Standard solution: 0.04 mg/mL of USP Car vedilol RS in *Mobile phase*
Sample solution: 0.04 mg/mL of Car vedilol 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 car vedilol and car vedilol related compound A
Tailing factor: NMT 1.5 for the car vedilol peak
Relative standard deviation: NMT 2%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of car vedilol ($C_{24}H_{26}N_2O_4$) 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 car vedilol from the *Sample solution*
r_S = peak response of car vedilol from the *Standard solution*
C_S = concentration of car vedilol in the *Standard solution* (mg/mL)
C_U = concentration of Car vedilol 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
- **Heavy Metals,** *Method II* ⟨231⟩**:** NMT 10 ppm
- **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 car vedilol 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 Car vedilol Related Compound C RS in *Mobile phase*
Standard solution: 1 µg/mL each of USP Car vedilol RS, USP Carvedilol Related Compound A RS, USP Car vedilol Related Compound B RS, USP Car vedilol Related Compound D RS, and USP Car vedilol Related Compound E RS, and 0.2 µg/mL of USP Car vedilol Related Compound C RS in *Mobile phase*
Sample solution: 1 mg/mL of Car vedilol 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 car vedilol related compound E, and use 240 nm for car vedilol 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 car vedilol and car vedilol related compound C
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of car vedilol related compound A, carvedilol related compound B, car vedilol related compound C, car vedilol related compound D, car vedilol related compound E, and any other individual impurity in the portion of Car vedilol 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 car vedilol.
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 Car vedilol 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

[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-yloxy)propan-2-ol).
[g] Disregard any impurity less than 0.01%.

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Table 1 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Carvedilol	1.0	—
Carvedilol related compound C [d]	3.6	0.02
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%.

- **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 Car vedilol System Suitability Mixture RS in *Diluent*
Sample solution: 1 mg/mL of Car vedilol 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 car vedilol and car vedilol 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-(6,7,8,9-tetrahydro-5*H*-carbazol-4-yloxy)propan-2-ol.
[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 Car vedilol System Suitability Mixture RS in *Diluent*
Sample solution: 1.5 mg/mL of Car vedilol in *Diluent* prepared as follows. Use about 1.9 mL of *Diluent* per mg of the Carvedilol, and sonicate briefly to facilitate dissolution.
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 car vedilol and car vedilol related compound F
Analysis
Sample: *Sample solution*
Calculate the percentage of car vedilol 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 car vedilol related compound F from the *Sample solution*
r_T = sum of the peak responses of car vedilol 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.

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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.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Carvedilol RS
  USP Carvedilol Related Compound A RS
  1-(4-(2-Hydroxy-3-(2-(2-methoxyphenoxy) ethylamino)propoxy)-9*H*-carbazol-9-yl)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol.
  $C_{36}H_{43}N_3O_7$ 629.74
  USP Carvedilol Related Compound B RS
  3,3′-(2-(2-Methoxyphenoxy)ethylazanediyl)bis(1-(9*H*-carbazol-4-yloxy)propan-2-ol).
  $C_{39}H_{39}N_3O_6$ 645.74
  USP Carvedilol Related Compound C RS
  1-(9*H*-Carbazol-4-yloxy)-3-(benzyl(2-(2-methoxyphenoxy)ethyl)amino)propan-2-ol.
  $C_{31}H_{32}N_2O_4$ 496.60
  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
  2-(2-Methoxyphenoxy)ethyl amine.
  $C_9H_{13}NO_2$ 167.21
  USP Carvedilol System Suitability Mixture RS
  Mixture of approximately 0.1% car vedilol related compound F (1-(2-(2-Methoxyphenoxy)ethylamino)-3-(2,3,4,9-tetrahydro-1*H*-carbazol-5-yloxy)propan-2-ol) in a matrix of car vedilol drug substance.

Carvedilol Tablets

DEFINITION

Carvedilol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of car vedilol ($C_{24}H_{26}N_2O_4$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩
  Wavelength range: 250–400 nm
  Cell: 0.2 cm
  Sample solution: 0.125 mg/mL of car vedilol prepared as follows. Place 10 Tablets in a 150-mL polypropylene tube, and disintegrate the Tablets in methanol (100 mL for the Tablet strengths 3.125, 6.25, and 25 mg, and 50 mL for the Tablet strength 12.5 mg) using a mechanical homogenizer. Transfer the homogenate to an appropriate volumetric flask, and dilute with methanol to volume. Pass through a suitable PTFE filter of 0.45-μm pore size.

ASSAY

- **PROCEDURE**
  Buffer: Dissolve 0.7 g of anhydrous monobasic potassium phosphate in 500 mL of water, and add 10 mL of triethylamine. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.
  Mobile phase: Dissolve 1.04 g of sodium dodecyl sulfate in 150 mL of *Buffer* in a 2-L volumetric flask, and sonicate. Add 720 mL of acetonitrile, and dilute with water to volume. Pass through a nylon 66 filter of 0.2-μm pore size.
  Diluent: Methanol and 1 M hydrochloric acid (9:1)
  Methanol solution: Methanol and water (1:1)
  Standard solution: 0.0125 mg/mL of USP Car vedilol RS prepared as follows. Dissolve a quantity of USP Car vedilol RS in a mixture of *Diluent* and water (9:1), and sonicate until the solution is clear. Dilute with *Methanol solution* to obtain the required final concentration.
  Sample stock solution: Transfer a portion of the powdered Tablets (NLT 20), equivalent to 25 mg of car vedilol, to a 100-mL volumetric flask. Add 10 mL of water, shake by hand, then add 70 mL of *Diluent*, and sonicate for 30 min. Shake on a mechanical shaker for about 30 min, and dilute with *Diluent* to volume to prepare a 0.25-mg/mL solution. Centrifuge an appropriate amount (about 50 mL) at 2000 rpm for 10 min.
  Sample solution: 0.0125 mg/mL of car vedilol in *Methanol solution* from the *Sample stock solution*. Pass a portion of the solution through a suitable syringe filter of 0.45-μm pore size, discard the first 5 mL, and use the filtrate as the *Sample solution*.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 240 nm
  Column: 4.6-mm × 50-mm; packing L7
  Column temperature: 40°
  Flow rate: 1 mL/min
  Run time: 30 min
  Injection size: 25 μL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of car vedilol ($C_{24}H_{26}N_2O_4$) 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 the *Standard solution* (mg/mL)
C_U = nominal concentration of the *Sample solution* (mg/mL)

  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨**711**⟩
  Test 1
  Medium: 0.7% (7 mL/L) of hydrochloric acid, adjusted with 50% (w/w) sodium hydroxide to a pH of 1.45 ± 0.2; 900 mL; deaerated
  Apparatus 2: 50 rpm
  Time: 30 min
  Standard stock solution: Transfer about 7 mg of USP Carvedilol RS to a 250-mL volumetric flask. Add 5 mL of methanol, and sonicate until dissolved. Cool to room temperature, dilute with *Medium* to volume, and mix well.
  Standard solution: On the basis of the label claim and using the *Standard stock solution*, prepare a solution of USP Carvedilol RS in *Medium* having an appropriate concentration (C_S), as shown in *Table 1*.

Table 1

Label Claim (mg)	C_S (mg/mL)
25	0.028
12.5	0.014
6.25	0.007
3.125	0.0035

  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

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