Carvedilol

![Structure of Carvedilol](image)

C₂₅H₂₆N₂O₄ 406.47
2-Propanol, 1-(9H-carbazol-4-yl oxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]- (±)-; (±)-1-(Carbazol-4-yl oxy)-3-[[2-(2-methoxyphen oxy)ethyl] amino]-2-propanol [72956-09-3]. is a potential impurity.

DEFINITION

Carvedilol contains NLT 98.0% and NMT 102.0% of C₂₅H₂₆N₂O₄, 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 Related Compound A RS and Carvedilol Related Compound E RS, and 0.2 µg/mL of USP Carvedilol Related Compound C RS in Mobile phase
  - **Standard solution:** 0.04 mg/mL of Carvedilol in Mobile phase
  - **Sample solution:** 0.04 mg/mL of carvedilol in Mobile phase

Chromatographic system

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** Dual wavelength, UV 220 nm and UV 240 nm.
- **Column:** 4.6-mm × 15-cm; 5-µm packing L7
- **Temperature:** 55°C
- **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 (C₂₅H₂₆N₂O₄) in the portion of the sample taken:**

\[
\text{Result} = \left( \frac{r_1}{r_2} \right) \times \left( \frac{C_4}{C_0} \right) \times 100
\]

\[r_0\] = peak response of carvedilol from the Sample solution

\[r_5\] = peak response of carvedilol from the Standard solution

\[C_0\] = concentration of carvedilol in the Sample solution (mg/mL)

\[C_4\] = 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 1.0 g
- **Heavy Metals, Method II (231):** NMT 10 ppm

Change to read:

- **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: Proceed 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 nm and UV 240 nm.
- **Column:** 4.6-mm × 15-cm; 5-µm packing L7
- **Temperature:** 55°C
- **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 the sample taken:**

\[
\text{Result} = \left( \frac{r_1}{r_2} \right) \times (C_4/C_0) \times 100
\]

\[r_0\] = peak response of the corresponding related compound or any other impurity from the Sample solution

\[r_5\] = peak response of the corresponding related compound from the Standard solution

\[C_0\] = concentration of carvedilol in the Standard solution (mg/mL)

\[C_4\] = concentration of the corresponding related compound in the Standard solution (mg/mL). To calculate the percentage of any other impurity, use the peak response of carvedilol.

\[C_0\] = concentration of Carvedilol RS.
Acceptance criteria: See Table 1.

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol related compound E</td>
<td>0.35</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol related compound A</td>
<td>0.52</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol related compound C</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Carvedilol related compound D</td>
<td>8.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol related compound B'</td>
<td>1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Carvedilol related compound F</td>
<td>1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol related compound A'</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>33</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>45</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>65</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>68</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>80</td>
<td>22</td>
<td>78</td>
</tr>
</tbody>
</table>

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

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:

Result = \((\frac{r_i}{r_s})\times100\)

where:
- \(r_i\) = peak response for each impurity in Sample solution
- \(r_s\) = sum of all the peak responses in Sample solution

Acceptance criteria: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol related compound A</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol related compound F</td>
<td>1.2</td>
<td>*</td>
</tr>
<tr>
<td>N-Isopropylcarvedilol</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Carvedilol related compound C</td>
<td>1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Carvedilol related compound B</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Biscarbazole</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Organic Impurities, Procedure 3: Carvedilol Related Compound F

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

**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: 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

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:

\[
\text{Result} = \left( \frac{r_0}{r_T} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \(r_0\) = 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 a 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
- USP Carvedilol Related Compound B RS
- USP Carvedilol Related Compound C RS
- USP Carvedilol Related Compound D RS
- USP Carvedilol Related Compound E RS

\[
\text{C}_{36}\text{H}_{43}\text{N}_{3}\text{O}_{7} \quad 629.74
\]
\[
\text{C}_{39}\text{H}_{39}\text{N}_{3}\text{O}_{6} \quad 645.74
\]
\[
\text{C}_{9}\text{H}_{13}\text{NO}_{2} \quad 167.21
\]
\[
\text{C}_{31}\text{H}_{32}\text{N}_{2}\text{O}_{4} \quad 496.60
\]
\[
\text{C}_{15}\text{H}_{13}\text{NO}_{2} \quad 239.27
\]

**Carvedilol**

\[
\begin{align*}
\text{C}_{30}\text{H}_{30}\text{N}_{3}\text{O}_{6} & \quad 629.74 \\
\text{C}_{39}\text{H}_{39}\text{N}_{3}\text{O}_{6} & \quad 645.74 \\
\text{C}_{9}\text{H}_{13}\text{NO}_{2} & \quad 167.21 \\
\text{C}_{31}\text{H}_{32}\text{N}_{2}\text{O}_{4} & \quad 496.60 \\
\text{C}_{15}\text{H}_{13}\text{NO}_{2} & \quad 239.27
\end{align*}
\]