Carvedilol Tablets

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

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 carvedilol 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 0.45-µm PTFE filter.

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 0.2-µm nylon 66 filter.
  Diluent: Methanol and 1 M hydrochloric acid (9:1)
  Methanol solution: Methanol and water (1:1)
  Standard solution: 0.0125 mg/mL of USP Carvedilol RS prepared as follows: Dissolve a quantity of USP Carvedilol 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 carvedilol, 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 carvedilol in *Methanol solution* from the *Sample stock solution*. Pass a portion of the solution through a suitable 0.45-µm syringe filter, 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
  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 carvedilol ($C_{24}H_{26}N_2O_4$) 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 in the *Standard solution* (mg/mL)
C_U = nominal concentration in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**
  Test 1
  Medium: •0.7% (7 mL/L)•(RB 1-Jan-2011) of hydrochloric acid adjusted •with 50% (w/w) sodium hydroxide•(RB 1-Jan-2011) 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* below.

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.
  Analytical wavelengths: 285 and 380 nm
  Path length: 1 cm
  Blank: *Medium*
  Analysis: Calculate the corrected absorbance of the *Standard solution* and the *Sample solution* as follows:

$$A_{corr} = A_{285} - A_{380}$$

A_{corr} = corrected absorbance of the *Standard solution* or the *Sample solution*
A_{285} = absorbance of the *Standard solution* or the *Sample solution* at 285 nm

A_{380} = absorbance of the *Standard solution* at 380 nm

Calculate the percentage of carvedilol dissolved as follows:

$$\text{Result} = (A_U/A_S) \times C_S \times (V/L) \times 100$$

A_U = corrected absorbance from the *Sample solution*
A_S = corrected absorbance from the *Standard solution*
C_S = corrected concentration of the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of carvedilol ($C_{24}H_{26}N_2O_4$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid without enzymes; 900 mL

Apparatus, Time, Standard stock solution, Standard solution, Sample solution, and **Analysis:** Proceed as directed for *Test 1*.

Tolerances: NLT 80% (*Q*) of the labeled amount of carvedilol ($C_{24}H_{26}N_2O_4$) is dissolved.

•**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: Simulated gastric fluid with pepsin, pH 1.45 (dissolve 12.0 g of sodium chloride and 19.2 g of purified pepsin (porcine origin, activity 800–2500 Units/mg of protein) in 18 mL of hydrochloric acid and sufficient water to make 6 L; adjust with hydrochloric acid to a pH of 1.45); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer: 2.72 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.0 ± 0.05.

Mobile phase: *Buffer* and acetonitrile (650:350)

Standard stock solution: 1.4 mg/mL of USP Carvedilol RS in methanol

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (L/900) mg/mL, where L is the Tablet label claim in mg.

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

Chromatographic system

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

Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-mm; 5-µm packing L7
Temperature: 35°
Flow rate: 1.5 mL/min
Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 3500 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis: Calculate the percentage of carvedilol dissolved:

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

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)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of carvedilol ($C_{24}H_{26}N_2O_4$) is dissolved. • (RB 1-Jan-2011)

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

Buffer, Mobile phase, Diluent, Methanol solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Sample solution: 0.25 mg/mL of carvedilol prepared as follows: Place 1 Tablet into a volumetric flask of appropriate size, based on the label claim. Add water to the flask up to about 10% of volume, and shake by hand to disintegrate the Tablet. Fill the flask up to 75% of volume with *Diluent*, and sonicate for 30 min to obtain complete disintegration. Shake on a mechanical shaker for 30 min, allow to cool, and dilute with *Diluent* to volume. Centrifuge an appropriate amount of this solution for 10 min at 2400 rpm, and transfer 4 mL of supernatant into a 100-mL volumetric flask. Fill the flask to about 85% of volume with *Methanol solution*, and sonicate for 20 min, with intermittent shaking. Dilute with *Methanol solution* to volume, and pass through a suitable 0.45-µm syringe filter.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of carvedilol ($C_{24}H_{26}N_2O_4$) in the Tablet 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)

IMPURITIES

• **ORGANIC IMPURITIES**

Buffer, Mobile phase, Diluent, and **Methanol solution:** Proceed as directed in the *Assay*.

Standard stock solution: Use the *Standard solution* from the *Assay*.

Standard solution: 1.25 µg/mL USP Carvedilol RS in a mixture of *Diluent* and water (1:1) from the *Standard stock solution*

Sample stock solution: Use the *Sample stock solution* from the *Assay*.

Sample solution: Dilute with water to volume, 25 mL of the supernatant from the *Sample stock solution* in a 50-mL volumetric flask. Pass a portion of the solution through a suitable 0.45-µm syringe filter.

Chromatographic system: Prepare as directed in the *Assay*.

Injection size: 15 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0
Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the Tablets taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of carvedilol from the *Standard solution*
C_S = concentration of USP Carvedilol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of carvedilol in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: NMT 0.2% (specified or unspecified)
Total impurities: NMT 1.0%

[NOTE—Disregard any peaks with a relative retention time less than or equal to 0.04 and peaks with less than 0.05%

of the nominal carvedilol peak response in the *Sample solution*.]

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers protected from moisture. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Carvedilol RS