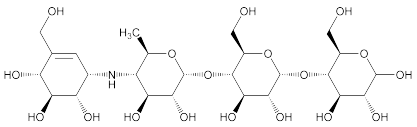
Acarbose



$C_{25}H_{43}NO_{18}$ 645.60

D-Glucose, *O*-4,6-dideoxy-4-[[[1*S*-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-;
O-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucose [56180-94-0].

DEFINITION

Acarbose is produced by certain strains of *Actinoplanes utahensis*. It contains NLT 95.0% and NMT 102.0% of acarbose ($C_{25}H_{43}NO_{18}$), calculated on the anhydrous 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**

Solution A: 0.6 mg/mL of monobasic potassium phosphate and 0.35 mg/mL of dibasic sodium phosphate in water

Mobile phase: Acetonitrile and *Solution A* (3:1)

System suitability solution: 20 mg/mL of USP Acarbose System Suitability Mixture RS in water

Standard solution: 20 mg/mL of USP Acarbose RS in water

Sample solution: 20 mg/mL of Acarbose in water

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4-mm × 25-cm; packing L8

Column temperature: 35°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Identify the acarbose peak and the peaks due to the impurities listed in *Table 1*.

Suitability requirements

Peak-to-valley ratio: The ratio of the height of the impurity A peak to the height of the valley between the impurity A peak and the acarbose peak is NLT 1.2.

Chromatogram comparability: The chromatogram obtained is similar to the chromatogram provided with USP Acarbose System Suitability Mixture RS for the known impurities found.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of acarbose ($C_{25}H_{43}NO_{18}$) in the portion of Acarbose 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 Acarbose RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩

Sample: 1.0 g

Acceptance criteria: NMT 0.2%

Delete the following:

- **Heavy Metals,** *Method II* ⟨231⟩**:** NMT 20 ppm (Official 1-Jan-2018)
- **Chromatographic Purity**

Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Diluted sample solution: Dilute 1.0 mL of the *Sample solution* with water to 100.0 mL.

Analysis

Samples: *Sample solution* and *Diluted sample solution*

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

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

r_U = peak response of each impurity from the *Sample solution*
r_A = peak response of the main acarbose peak from the *Diluted sample solution*
F = relative response factor for each impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Impurity A[a]	0.9	1	0.6
Impurity B[b]	0.8	1.6	0.5
Impurity C[c]	1.2	1	1.5
Impurity D[d]	0.5	1.33	1.0
Impurity E[e]	1.7	0.8	0.2
Impurity F[f]	1.9	0.8	0.3
Impurity G[g]	2.2	0.8	0.3
Impurity H[h]	0.6	1	0.2

[a] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-arabino-hex-2-ulopyranose.

[b] (1*R*,4*R*,5*S*,6*R*)-4,5,6-Trihydroxy-2-(hydroxymethyl)cyclohex-2-enyl 4-*O*-[4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-α-D-glucopyranoside.

[c] α-D-Glucopyranosyl 4-*O*-[4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-α-D-glucopyranoside.

[d] 4-*O*-[4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-D-glucopyranose.

[e] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-arabino-hex-2-ulopyranose (4-*O*-α-acarbosyl-D-fructopyranose).

[f] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose (4-*O*-α-acarbosyl-D-glucopyranose).

[g] α-D-Glucopyranosyl *O*-4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranoside (α-D-glucopyranosyl α-acarboside).

[h] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-6-deoxy-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

Table 1 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any individual unknown impurity	—	—	0.2
Total impurities	—	—	3.0

[a] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-arabino-hex-2-ulopyranose.

[b] (1*R*,4*R*,5*S*,6*R*)-4,5,6-Trihydroxy-2-(hydroxymethyl)cyclohex-2-enyl 4-*O*-[4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-α-D-glucopyranoside.

[c] α-D-Glucopyranosyl 4-*O*-[4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-α-D-glucopyranoside.

[d] 4-*O*-[4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl]-D-glucopyranose.

[e] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-arabino-hex-2-ulopyranose (4-*O*-α-acarbosyl-D-fructopyranose).

[f] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose (4-*O*-α-acarbosyl-D-glucopyranose).

[g] α-D-Glucopyranosyl *O*-4,6-dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranoside (α-D-glucopyranosyl α-acarboside).

[h] *O*-4,6-Dideoxy-4-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino}-α-D-glucopyranosyl-(1→4)-*O*-6-deoxy-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

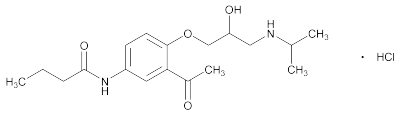
SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨**781S**⟩
  Sample solution: 10 mg/mL in water
  Acceptance criteria: +168° to +183°
- **pH** ⟨**791**⟩
  Sample solution: 50 mg/mL
  Acceptance criteria: 5.5–7.5
- **Water Determination,** *Method Ic* ⟨**921**⟩**:** NMT 4.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards** ⟨**11**⟩
  USP Acarbose RS
  USP Acarbose System Suitability Mixture RS

Acebutolol Hydrochloride



$C_{18}H_{28}N_2O_4 \cdot HCl$ 372.89

Butanamide, *N*-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-, monohydrochloride, (±)-;
(±)-3′-Acetyl-4′-[2-hydroxy-3-(isopropylamino)propoxy]-butyranilide monohydrochloride [34381-68-5].

DEFINITION

Acebutolol Hydrochloride contains NLT 98.0% and NMT 102.0% of acebutolol hydrochloride ($C_{18}H_{28}N_2O_4 \cdot HCl$), 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*.
- **C. Identification Tests—General,** *Chloride* ⟨**191**⟩**:** Meets the requirements when tested as directed for alkaloidal hydrochlorides

ASSAY

- **Procedure**

Mobile phase: Methanol, glacial acetic acid, and 0.3% aqueous solution of sodium dodecyl sulfate (675:20:325). Make adjustments if necessary to achieve a retention time for acebutolol of between 4 and 7 min.

Standard solution: 0.14 mg/mL of USP Acebutolol Hydrochloride RS in water

Sample solution: 0.14 mg/mL of Acebutolol Hydrochloride in water

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 30-cm; packing L1
Flow rate: 2 mL/min
Injection volume: 10 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 1500 theoretical plates
Tailing factor: NMT 2.5
Relative standard deviation: 0.73%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of acebutolol hydrochloride ($C_{18}H_{28}N_2O_4 \cdot HCl$) in the portion of Acebutolol Hydrochloride taken:

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

r_U = peak response of acebutolol from the *Sample solution*
r_S = peak response of acebutolol from the *Standard solution*
C_S = concentration of USP Acebutolol Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Acebutolol Hydrochloride in the *Sample solution* (mg/mL)

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

IMPURITIES

- **Residue on Ignition** ⟨**281**⟩**:** NMT 0.1%

Delete the following:

- **Heavy Metals,** *Method II* ⟨**231**⟩**:** NMT 20 ppm (Official 1-Jan-2018)

- **Organic Impurities**

Solution A: Mix 2.0 mL of phosphoric acid and 3.0 mL of triethylamine, and dilute with water to 1 L.

Solution B: Acetonitrile and *Solution A* (1:1)

Standard stock solution 1: 0.2 mg/mL of USP Acebutolol Related Compound A RS prepared as follows. Dissolve a suitable amount of USP Acebutolol Related Compound A RS in a suitable volumetric flask, in 50% of the total volume of acetonitrile, and dilute with *Solution A* to volume.

Standard stock solution 2: 0.2 mg/mL of USP Acebutolol Related Compound B RS prepared as follows. Dissolve a suitable amount of USP Acebutolol Related Compound B RS in a suitable volumetric flask, in 50% of the total volume of acetonitrile, and dilute with *Solution A* to volume.