Dapagliflozin Propanediol Monohydrate

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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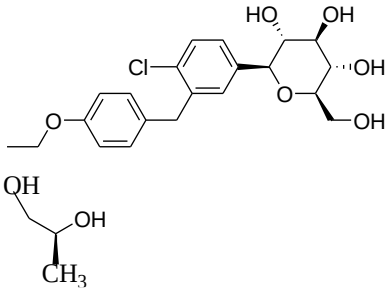
Dapagliflozin Propanediol Monohydrate



.H_2O

$C_{24}H_{35}ClO_9$ Mol. Wt. 503.0

Dapagliflozin propanediol monohydrate is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;(2S)-propane-1,2-diol;hydrate.

Dapagliflozin propanediol monohydrate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{24}H_{35}ClO_9$, calculated on the anhydrous basis.

Category. Antidiabetic.

Description. A white to off white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dapagliflozin propanediol monohydrate IPRS* or with the reference spectrum of dapagliflozin propanediol monohydrate.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

(S)-1,2-Propanediol Content. 13.0 per cent to 17.0 per cent,

Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.16 per cent v/v solution of *1-pentanol* in *acetonitrile*.

Test solution. Dissolve 0.2 g of the substance under examination in the internal standard solution with the aid of ultrasound and dilute to 10.0 ml with the internal standard solution.

Reference solution (a). A 0.3 per cent w/v solution of *(S)-1,2-Propanediol IPRS* in the internal standard solution.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the internal standard solution.

Chromatographic system
- a capillary column 30 m x 0.53 mm, packed with nitro-terephthalic acid modified polyethylene glycol as stationary phase (film thickness 1.0 µm) (Such as DB-FFAP),
- temperature:
  column 60° for 5 minutes, 60° to 140° @ 10° per minute and hold at 140° for 4 minutes. 140° to 230° @ 45° per minute and hold at 230° for 20 minutes

- inlet port at 220º and detector at 280º,
- flame ionization detector,
- split ratio: 20:1,
- flow rate: 5 ml per minute using nitrogen as carrier gas.
- injection volume: 1 µl,

Name	Relative retention time
Acetonitrile	0.25
1-pentanol	0.61
(S)-1,2-Propanediol	1.00

Inject reference solution (a) and (b). The test is not valid unless the relative standard deviation of the ratio of peak area of (S)-1,2-propanediol to that of peak area of 1-pentanol (internal standard) for replicate injections is not more than 15.0 per cent in the chromatogram obtained with reference solution (a) and the signal to noise ratio for (S)-1,2-propanediol peak is not less than 10 in the chromatogram obtained with reference solution (b).

Inject the reference solution and the test solution.

Calculate the content of (S)-1,2-Propanediol using ratio of the peak area of (S)-1,2-Propanediol to that of peak area of the (1-pentanol) internal standard.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *acetonitrile* and *water*.

Buffer solution. Dissolve 1.15 g of *ammonium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 5.0 with *dilute ammonia solution*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.0005 per cent w/v solution of *dapagliflozin propanediol monohydrate IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.00012 per cent w/v, each of, *ortho isomer of dapagliflozin impurity IPRS* and *dapagliflozin dimer-1 impurity IPRS* and 0.08 per cent w/v of *dapagliflozin propanediol monohydrate IPRS* in the solvent mixture.

Reference solution (c). Dilute 2.0 ml of reference solution (a) to 25.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 10 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (2.6 µm) (Such as Kinetex XB-C 18),
- mobile phase: A. a mixture of 90 volumes of the buffer solution and 10 volumes of *acetonitrile*,
  B. a mixture of 20 volumes of the buffer solution and 80 volumes of *acetonitrile*,
- flow rate: 0.8 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20

50	10	90
75	10	90
77	80	20
85	80	20

Name	Relative retention time	Correction factor
Dapagliflozin propanediol monohydrate	1.0	---
Ortho isomer of Dapagliflozin[1]	1.06	1.12
Alpha isomer of Dapagliflozin[2]	1.14	0.91
Dapagliflozin diamer-1[3]	1.56	0.92
Dapagliflozin dimer-2[4]	2.23	1.03
Acetyl Dapagliflozin [5]	2.93	1.29

[1](1S)-1,5-anhydro-1-C-{4-chloro-3-[(2-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[2](1R)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[3](2S,3R,4R,5S,6R)-2-[4-chloro-3-[(5-{2-Chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]benzyl]-2-ethoxyphenyl)(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
[4](1S)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-6-O-[1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}D-glucopyranosyl]-D-glucitol.
[5](1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]-phenyl}-D-glucitol.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to dapagliflozin and ortho isomer of dapagliflozin is not less than 3.0 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 28000 theoretical plates, the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 20 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ortho isomer of dapagliflozin, alpha isomer of dapagliflozin, dapagliflozin diamer-1, dapagliflozin dimer-2 and acetyl dapagliflozin, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). the area of any other secondary peak is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (2.3.13). 2.0 g complies with limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Water (2.3.43). 3.2 per cent to 4.8 per cent, determined on 0.5 g.

Assay. Determine by liquid chromatography (2.4.14),

Solvent mixture. Equal volumes of *acetonitrile* and *water*.

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.006 per cent w/v solution of *dapagliflozin propanediol monohydrate IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Kromasil C 18),
- mobile phase: a mixture of 55 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *orthophosphoric acid* and 45 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{24}H_{35}ClO_9$.

Storage. Store protected from moisture, at a temperature not exceeding 30°.

Dapagliflozin Propanediol Monohydrate:

Solubility: Soluble in *ethanol (95 per cent)*, slightly soluble in *water* and practically insoluble in *hexane*.