Dapagliflozin Tablets

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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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Further follow-up action as required.	

Dapagliflozin Tablets

Dapagliflozin Propanediol Monohydrate Tablets

Dapagliflozin Tablets contain dapagliflozin propanediol monohydrate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of dapagliflozin, $C_{21}H_{25}ClO_6$.

Usual strengths. 5 mg; 10 mg.

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 reference solution.

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 1000 ml of acetate buffer 4.5, prepared by dissolving 2.99 g of *sodium acetate trihydrate* and 1.6 ml of *glacial acetic acid* in 1000 ml of *water*, adjusted to pH 4.5 with *glacial acetic acid*.
Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

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

Test solution. Use the filtrate, dilute if necessary, with dissolution medium.

Reference solution. A solution of *dapagliflozin propanediol monohydrate IPRS* containing 0.025 per cent w/v of dapagliflozin in the solvent mixture. Dilute 2.0 ml of the solution to 100.0 ml with the dissolution medium.

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),
- sample temperature: 10°
- mobile phase: a mixture of 60 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 40 volumes of *acetonitrile*,
- flow rate: 1.4 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 50 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3500 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{25}ClO_6$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{21}H_{25}ClO_6$.

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. Disperse a quantity of the powdered tablets containing 25 mg of Dapagliflozin in 25 ml of *acetonitrile*, with the aid of ultrasound with intermittent shaking and dilute to 50.0 ml with *water*, filter.

Reference solution. A solution of *dapagliflozin propanediol monohydrate IPRS* containing 0.00025 per cent w/v of dapagliflozin in 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
Desethyl dapagliflozin[1]	0.37	1.02
Hydroxy dapagliflozin[2]	0.51	1.11
Oxo dapagliflozin[3]	0.72	1.29
Dapagliflozin (Retention time: about 13 minutes)	1.0	---
Ortho isomer of dapagliflozin[4*]	1.07	---
Alpha isomer of dapagliflozin[5*]	1.14	---
Dapagliflozin diamer-1[6*]	1.57	---
Dapagliflozin dimer-2[7*]	2.25	---
Acetyl dapagliflozin[8*]	3.00	---

[*]Process impurity included for identification only and not included in the calculation of total degradation products,
[1](2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
[2](2S,3R,4R,5S,6R)-2-(4-Chloro-3-((4-ethoxyphenyl)(hydroxy)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol.
[3](2-Chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)phenyl)(4-ethoxyphenyl)methanone.
[4](1S)-1,5-anhydro-1-C-{4-chloro-3-[(2-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[5](1R)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[6](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.
[7](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.
[8](1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]-phenyl}-D-glucitol.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 28000 theoretical plates and the tailing factor is not more than 1.5,

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to desethyl dapagliflozin, hydroxy dapagliflozin and oxo dapagliflozin, each of, is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent). the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with the reference solution (2.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Uniformity of content. Complies with the test stated under Tablets.

Determine by liquid chromatography (2.4. 14), as described under Assay, using the following modifications.

Test solution. Transfer one intact tablet to a 100-ml volumetric flask, add 50 ml of *water*. Stir for 30 minutes or till complete dispersion of tablet. Add 35 ml of *acetonitrile* and sonicate for 30 minutes with intermittent shaking, dilute to volume with *acetonitrile*, filter. Dilute, if necessary with the solvent mixture.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3500 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{25}ClO_6$ in the tablet.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

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

Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing 50 mg of Dapagliflozin in 50 ml of *water*. Stir for 30 minutes, add 35 ml of *acetonitrile* and sonicate for 30 minutes with intermittent shaking and dilute to 100.0 ml with *acetonitrile*, filter. Dilute 5.0 ml of the filtrate to 50.0 ml with the solvent mixture.

Reference solution. A solution of *dapagliflozin propanediol monohydrate IPRS* containing 0.005 per cent w/v of dapagliflozin 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 60 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 40 volumes of *acetonitrile*,
- flow rate: 1.4 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 3500 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{25}ClO_6$ in the tablets.

1 mg of dapagliflozin propanediol monohydrate $C_{24}H_{35}ClO_9$ is equivalent to 0.843 mg of dapagliflozin, $C_{21}H_{25}ClO_6$.

Labelling. The label states the strength in terms of the equivalent amount of dapagliflozin.

Storage. Store at temperature not exceeding 30º.