Dapagliflozin and Sitagliptin 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.

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Dapagliflozin and Sitagliptin Tablets

Dapagliflozin Propanediol Monohydrate and Sitagliptin Phosphate Tablets

Dapagliflozin and Sitagliptin Tablets contain dapagliflozin propanediol monohydrate and Sitagliptin Phosphate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of dapagliflozin, $C_{21}H_{25}ClO_6$ and Sitagliptin, $C_{16}H_{15}F_6N_5O$.

Usual strengths. Dapagliflozin, 5 mg and Sitagliptin, 50 mg; Dapagliflozin, 5 mg and Sitagliptin, 100 mg, Dapagliflozin, 10 mg and Sitagliptin, 50 mg; Dapagliflozin, 10 mg and Sitagliptin, 100 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution (a) and test solution (b) correspond to the peaks in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium. 1000 ml of a buffer solution 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).

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

Reference solution (a). Weight and transfer *dapagliflozin propanediol monohydrate IPRS* equivalent to 25mg of dapagliflozin to a 250-ml volumetric flask, add 20 ml of *methanol* and sonicate for 5 minutes with intermittent shaking, add 100 ml of dissolution medium and further sonicate for 2 minutes with intermittent shaking, dilute to volume with dissolution medium.

Reference solution (b). Weight and transfer *sitagliptin phosphate IPRS* equivalent to 50 mg of sitagliptin to a 100-ml volumetric flask, add 10 ml of *methanol* and sonicate for 5 minutes with intermittent shaking, add 70 ml of dissolution medium and further sonicate for 2 minutes with intermittent shaking, dilute to volume with dissolution medium.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with the dissolution medium to obtain a solution having similar concentration to the test solution.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS 3V),
- sample temperature: 10°,
- column temperature: 40º,
- mobile phase: A. a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid*.
  B. a mixture of 62.5 volumes of *methanol* and 37.5 volumes of acetonitrile,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	55	45
3	55	45
8	20	80
13	20	80
15	55	45
20	55	45

Inject the reference solution (c). The test is not valid unless 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, for both peaks.

Inject reference solution (c) and the test solution.

Calculate the content of $C_{21}H_{25}ClO_6$ and $C_{16}H_{15}F_6N_5O$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{21}H_{25}ClO_6$ and $C_{16}H_{15}F_6N_5O$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *water* and 60 volumes of *methanol*.

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. Transfer a quantity of the powdered tablets containing 25 mg of Dapagliflozin to a 250-ml volumetric flask, add 100 ml of *water* and sonicate for 30 minutes with intermittent shaking, add 100 ml of *methanol* and further sonicate for 30 minutes with intermittent shaking, dilute to volume with *methanol*, filter.

Reference solution. A solution of *dapagliflozin propanediol monohydrate IPRS* containing 0.0001 per cent w/v of dapagliflozin and *sitagliptin phosphate IPRS* containing 0.001 per cent w/v of sitagliptin 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),
- sample temperature: 10°,
- column temperature: 30º,
- 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*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
50	10	90
75	10	90
77	90	10
85	90	10

Name	Relative	Correction

	retention time	factor
Sitagliptin	0.37	---
Desethyl dapagliflozin[1]	0.52	0.96
Hydroxy dapagliflozin[2]	0.65	1.12
Oxo dapagliflozin[3]	0.81	1.09
Dapagliflozin	1.0	---
Ortho isomer of dapagliflozin[4*]	1.04	---
Alpha isomer of dapagliflozin[5*]	1.10	---
Dapagliflozin diamer-1[6*]	1.37	---
Dapagliflozin dimer-2[7*]	1.79	---
Acetyl dapagliflozin[8*]	2.24	---

*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 8000 theoretical plates for sitagliptin and 50000 theoretical plates for dapagliflozin peak and the tailing factor is not more than 1.5, for both the peaks.

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 the area of the dapagliflozin peak in the chromatogram obtained with the reference solution (1.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the dapagliflozin peak in the chromatogram obtained with the reference solution (0.5 per cent) and sum of all the secondary peaks other than hydroxy dapagliflozin and oxo dapagliflozin is not more than twice the area of the dapagliflozin peak in the chromatogram obtained with the reference solution (2.0 per cent). Ignore the peaks due to sitagliptin.

Uniformity of dosage units (2.5.4). Meet the requirements.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *water* and 60 volumes of *methanol*.

Test solution. Transfer a quantity of the powdered tablets containing 500 mg of sitagliptin to a 250-ml volumetric flask, add 100 ml of *water* and sonicate for 30 minutes with intermittent shaking, add 100 ml of *methanol* and further sonicate for 30 minutes with intermittent shaking, dilute to volume with *methanol*, filter. Dilute 5.0 ml of the filtrate to 50.0 ml with the solvent mixture.

Reference solution (a). A solution containing *dapagliflozin propanediol monohydrate IPRS* containing 0.01 per cent w/v of dapagliflozin in the solvent mixture.

Reference solution (b). A solution containing *sitagliptin phosphate IPRS* containing 0.1 per cent w/v of sitagliptin in the solvent mixture.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with the solvent mixture to obtain a solution having concentration similar to the test solution.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS 3V),
- sample temperature: 10°,

- column temperature: 40º,
- mobile phase: : A. a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid*,
  B. a mixture of 62.5 volumes of *methanol* and 37.5 volumes of acetonitrile,
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	55	45
3	55	45
8	20	80
13	20	80
15	55	45
20	55	45

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 20000 theoretical plates for dapagliflozin and 2000 theoretical plates for sitagliptin, 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, for both the peaks.

Inject reference solution (c) and the test solution.

Calculate the content of $C_{21}H_{25}ClO_6$ and $C_{16}H_{15}F_6N_5O$ in the tablets.

1 mg of dapagliflozin propanediol monohydrate $C_{24}H_{35}ClO_9$ is equivalent to 0.843 mg of dapagliflozin, $C_{21}H_{25}ClO_6$ and 1 mg of sitagliptin phosphate $C_{16}H_{18}F_6N_5O_5P$, H_2O is equivalent to 0.806 mg of sitagliptin, $C_{16}H_{15}F_6N_5O$.

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

Storage. Store at temperature not exceeding 30º.