Dapagliflozin Propanediol Monohydrate and Metformin Hydrochloride Prolonged-release 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. 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 Propanediol Monohydrate and Metformin Hydrochloride Prolonged-release Tablets

Dapagliflozin Propanediol Monohydrate and Metformin Hydrochloride Sustained-release Tablets; Dapagliflozin Propanediol Monohydrate and Metformin Hydrochloride Extended-release Tablets; Dapagliflozin Propylene Glycol Monohydrate and Metformin Hydrochloride Sustained-release Tablets; Dapagliflozin Propylene Glycol Monohydrate and Metformin Hydrochloride Extended-release Tablets; Dapagliflozin Propylene Glycol Monohydrate and Metformin Hydrochloride Prolonged-release Tablets.

Dapagliflozin Propanediol Monohydrate and Metformin Hydrochloride Prolonged-release 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 amounts of dapagliflozin, $C_{21}H_{25}ClO_6$ and metformin hydrochloride, $C_4H_{11}N_5$,HCl.

Dapagliflozin Propanediol Monohydrate and Metformin Hydrochloride Prolonged-release Tablets manufactured by different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable, as the dissolution profile of the products of different manufacturers may not be the same.

Usual strengths. Dapagliflozin 5 mg and Metformin hydrochloride 500 mg; Dapagliflozin 5 mg and Metformin hydrochloride 1000 mg; Dapagliflozin 10 mg and Metformin hydrochloride 500 mg; Dapagliflozin 10 mg and Metformin hydrochloride 1000 mg.

Identification

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

Tests

Dissolution (2.5.2).

For dapagliflozin —

Apparatus No. 1 (Basket),
Medium. 1000 ml of a buffer solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute sodium hydroxide solution*,
Speed and time. 100 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. 85 volumes of mobile phase A and 15 volumes of *acetonitrile*.

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

Reference solution. A solution of *dapagliflozin propanediol monohydrate IPRS* in the solvent mixture containing 0.05 per cent w/v of dapagliflozin. Dilute 1.0 ml of the solution to 100.0 ml with the dissolution medium. *(NOTE – sonicate to dissolve, if necessary)*.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with base-deactivated octadecylsilane bonded to porous silica (5 µm) (such as Thermo BDS C18),
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 205 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile Phase B (per cent v/v)
0	85	15
12	50	50

17	50	50
20	85	15
25	85	15

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 2.0 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 $C_{21}H_{25}ClO_6$.

For metformin hydrochloride — Complies with the test stated under Tablets.

Related substances. Determine by liquid chromatography (2.4.14).

For dapagliflozin —

Solvent mixture. 85 volumes of *acetonitrile* and 15 volumes of *water*.

Test solution. Disperse a quantity of the powdered tablets containing equivalent to 20 mg of Dapagliflozin in 20 ml of *methanol*, with the aid of ultrasound for 5 minutes. Add 130 ml of the solvent mixture, further sonicate for 10 minutes with intermittent shaking and dilute to 200.0 ml with the solvent mixture. Dilute 10.0 ml of the solution to 20.0 ml with the solvent mixture. Centrifuge a portion of the solution at 3500 rpm for 15 minutes and filter the supernatant liquid, use filtrate.

Reference solution. Dissolve a quantity of *dapagliflozin propanediol monohydrate IPRS* containing 25 mg of dapagliflozin in 20 ml of *methanol*, with the aid of ultrasound for 3 minutes. Add 50 ml of the solvent mixture, further sonicate 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. Further dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (such as Intersil C18),
- column temperature: 40°,
- mobile phase: A. a mixture of 80 volumes of a buffer solution prepared by dissolving 0.96 g of *sodium pentanesulphonate* in 1000 ml of *water*, adjusted to pH 2.5 with *orthophosphoric acid* and 20 volumes of *acetonitrile*,
  B. a mixture of 20 volumes of *water*, 80 volumes of *acetonitrile* and 0.1 volumes of 3 per cent v/v solution of *trifluoroacetic acid* in *water*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile Phase B (per cent v/v)
0	65	35
10	65	35
30	30	70
75	20	80
76	65	35
80	65	35

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any 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 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 peaks due to metformin hydrochloride and metformin hydrochloride related impurities.

For metformin hydrochloride —

Solvent mixture. 2.5 volumes of *acetonitrile* and 100 volumes of *water*.

Test solution. Disperse a quantity of the powdered tablets containing about 0.5 g of Metformin Hydrochloride in 10 ml of *methanol*, with the aid of ultrasound for 10 minutes. Add 60 ml of the solvent mixture, further sonicate for 10 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 100.0 ml with the solvent mixture, filter.

Reference solution (a). A 0.00125 per cent w/v solution of *metformin hydrochloride IPRS* in the solvent mixture. *(NOTE – sonicate to dissolve, if necessary)*.

Reference solution (b). A 0.0005 per cent w/v solution of *dicyandiamide IPRS* in the solvent mixture. *(NOTE – sonicate to dissolve, if necessary)*.

Reference solution (c). Transfer 2.0 ml of reference solution (a) and 1.0 ml of reference solution (b) into a 100-ml volumetric flask and dilute to volume with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Waters Xterra RP-18),
- column temperature: 30°,
- mobile phase: A. a buffer solution prepared by dissolving 0.5 g of *sodium heptanesulphonate* and 0.5 g of *sodium chloride* in 1000 ml of *water*, adjusted to pH 3.8 with *0.06 M orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 218 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile Phase B (per cent v/v)
0	92	8
10	92	8
17	50	50
21	50	50
27	25	75
32	25	75
33	92	8
40	92	8

Name	Relative retention time
Dicyandiamide[1]	0.48
Metformin (Retention time: about 9.2 minutes)	1.0

[1]2-cyanoguanidine.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to dicyandiamide and metformin is not less than 2.0, the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections for dicyandiamide is not more than 10.0 per cent and for metformin, not more than 5.0 per cent.

Inject reference solution (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to dicyandiamide is not more than the area of corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent) and the area of any other secondary peak is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Microbial contamination (2.2.9). Total aerobic viable count is not more than 10^3 CFU per g and total combined molds and yeasts count is not more than 10^2 CFU per g determined by plate count. 1 g is free from *Escherichia coli*.

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14), as described under Dissolution (*For dapagliflozin*) with the following modifications.

Test solution (a). Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing about 500 mg of Metformin Hydrochloride in 60 ml of *methanol*, with the aid of ultrasound for 30 minutes with intermittent shaking and dilute to 100.0 ml with *methanol*, filter.

Test solution (b). Dilute a suitable volume of test solution (a) with the solvent mixture to obtain a solution containing 0.0005 per cent w/v of Dapagliflozin.

Test solution (c). Dilute a suitable volume of test solution (a) with the solvent mixture to obtain a solution containing 0.0025 per cent w/v of Metformin Hydrochloride.

Reference solution (a). Dissolve a quantity of *dapagliflozin propanediol monohydrate IPRS* in *methanol* containing 0.025 per cent w/v of dapagliflozin. *(NOTE – sonicate to dissolve, if necessary)*.

Reference solution (b). A 0.025 per cent w/v solution of *metformin hydrochloride IPRS* in *methanol*. *(NOTE – sonicate to dissolve, if necessary)*.

Reference solution (c). Transfer 2.0 ml of reference solution (a) to a 100-ml volumetric flask, add 10.0 ml of reference solution (b) and dilute to volume with the solvent mixture.

Chromatographic system

– injection volume: 10 µl.

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 1000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject reference solution (c) and test solution (b) (for dapagliflozin) and (c) (for metformin hydrochloride).

Calculate the content of $C_{21}H_{25}ClO_6$ in test solution (b) and $C_4H_{11}N_5$,HCl in test solution (c) in the tablets.

1 mg of dapagliflozin propanediol monohydrate, $C_{21}H_{25}ClO_6$,$C_3H_8O_2$,H_2O is equivalent to 0.8129 mg of dapagliflozin, $C_{21}H_{25}ClO_6$.

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

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