Dapagliflozin 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. 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 Metformin Hydrochloride Prolonged-release Tablets

Dapagliflozin and Metformin Hydrochloride Sustained-release Tablets; Dapagliflozin and Metformin Hydrochloride Extended-release Tablets.

Dapagliflozin and Metformin Hydrochloride Prolonged-release Tablets contain 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 metformin hydrochloride, $C_4H_{11}N_5$, HCl.

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 of Dapagliflozin and Metformin hydrochloride the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).

For Dapagliflozin —

Apparatus No. 1 (Basket),
Medium. 1000 ml of phosphate buffer pH 6.8, prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.
Speed and time. 100 rpm and 20 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 the dissolution medium.

Reference solution. Weight and transfer 25 mg of *dapagliflozin IPRS* to a 100-ml volumetric flask, add 10 ml of *acetonitrile*, sonicate for 5 minutes to dissolve and dilute to volume with the dissolution medium. 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 C18),
- column temperature: 30º,
- sample temperature: 25°,
- mobile phase: a mixture of 65 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 *dilute orthophosphoric acid* and 35 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 4000 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 80 per cent of the stated amount of $C_{21}H_{25}ClO_6$.

For Metformin Hydrochloride —

Apparatus No. 1 (Basket),
Medium. 1000 ml of phosphate buffer pH 6.8, prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.

Speed and time. 100 rpm and 1 hour, 3 hours and 10 hours.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of the filtrate with the dissolution medium to obtained a solution containing 0.004 per cent w/v of metformin hydrochloride.

Reference solution. A 0.004 per cent w/v solution of *metformin hydrochloride IPRS* in the dissolution medium.

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),
- column temperature: 30º,
- sample temperature: 25°,
- mobile phase: a mixture of 95 volumes of a buffer solution prepared by dissolving 0.94 g of *sodium pentane sulphonic acid sodium salt monohydrate* in 1000 ml of *water*, adjusted to pH 3.5 with *dilute orthophosphoric acid* and 5 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 233 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 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 $C_4H_{11}N_5$, HCl in the medium.

The percentages of the labeled amount of metformin hydrochloride, $C_4H_{11}N_5$, HCl dissolved at the times specified confirm to 2.5.2. Dissolution test. Acceptance Table 2.

At 1 hour, not less than 22.0 per cent and not more than 42.0 per cent; at 3 hours, not less than 51.0 per cent and not more than 71.0 per cent; and at 10 hours, not less than 85.0 per cent.

Related substances. Determine by liquid chromatography (2.4.14).

For Dapagliflozin —

Buffer solution A. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.

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

Solvent mixture. 40 volumes of *methanol* and 60 volumes of buffer solution A

Test solution. Transfer sufficient quantity of intact tablets containing 100 mg of Dapagliflozin to a 500-ml volumetric flask, add 50 ml of buffer solution A, stir on magnetic stirrer for 10 minutes, add 300 ml of *methanol*, further stir on magnetic stirrer for 2 hours and dilute to volume with *methanol*, allow to stand for 10 minutes. Centrifuge a portion of the solution at 10000 rpm for 10 minutes. Dilute 10.0 ml of the supernatant liquid to 25.0 ml with buffer solution A, filter. *[Note—Stirring time can be increased to ensure complete dispersion of tablets]*.

Reference solution (a). Dissolve 40 mg of *dapagliflozin IPRS* in 70 ml of solvent mixture with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 100.0 ml with solvent mixture. Further dilute 2.0 ml of the solution to 50.0 ml with solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 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),
- column temperature: 35º,
- sample temperature: 10°,
- mobile phase: A. a mixture of 90 volumes of buffer solution B and 10 volumes of *acetonitrile*,
  B. a mixture of 20 volumes of buffer solution B and 80 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.8 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	80	20
50	10	90
75	10	90
77	80	20
85	80	20

Name	Relative retention time	Correction factor
Metformin	0.09	---
Cyanoguanidine	0.10	---
Desethyl dapagliflozin[1]	0.37	1.07
Hydroxy dapagliflozin[2]	0.52	1.16
Dapagliflozin carboxylic acid[3]	0.54	1.67
Oxo dapagliflozin[4]	0.72	1.25
Dapagliflozin (Retention time: about 13 minutes)	1.0	---
Ortho isomer of dapagliflozin[5*]	1.07	---
Alpha isomer of dapagliflozin[6*]	1.15	---
Dapagliflozin diamer-1[7*]	1.60	---
Dapagliflozin dimer-2[8*]	2.30	---
Acetyl dapagliflozin[9*]	2.98	---

[*]Process impurity included for identification only and not to be 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](6S)-2,6-anhydro-6-[4-chloro-3-(4-ethoxybenzyl)phenyl]-L-gulonic acid.
[4](2-Chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)phenyl)(4-ethoxyphenyl)methanone.
[5](1S)-1,5-anhydro-1-C-{4-chloro-3-[(2-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[6](1R)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[7](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.
[8](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.
[9](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) and (b). The test is not valid unless the column efficiency is not less than 28000 theoretical plates, the tailing factor is not more than 1.5 and 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 (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to desethyl dapagliflozin, hydroxy dapagliflozin, oxo dapagliflozin and dapagliflozin carboxylic acid, each of, is not more than 0.5 times 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 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is

not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent). Ignore the peaks due to metformin hydrochloride and metformin hydrochloride related impurities.

For Metformin Hydrochloride —

Buffer solution. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.

Test solution. Transfer sufficient quantity of intact tablets containing 5 g of Metformin hydrochloride to a 250-ml volumetric flask, add 25 ml of the buffer solution, stir on magnetic stirrer for 10 minutes. Add 150 ml of *methanol*, further stir on magnetic stirrer for 2 hours and dilute to volume with *methanol*, allow to stand for 10 minutes. Centrifuge a portion of the solution at 10000 rpm for 10 minutes. Dilute 5.0 ml of supernatant liquid to 100.0 ml with buffer solution, filter. *[Note—Stirring time can be increased to ensure complete dispersion of tablets]*.

Reference solution (a). Dissolve 40 mg of *metformin hydrochloride IPRS* in70 ml of the buffer solution with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the buffer solution. Dilute 5.0 ml of the solution to 200.0 ml with the buffer solution.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the buffer 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),
- column temperature: 30º,
- sample temperature: 25°,
- mobile phase: A. a buffer solution prepared by dissolving 0.96 g of *1-pentanesulphonic acid sodium salt monohydrate* and 0.8 g of *1- butane sulphonic acid sodium salt* in 1000 ml of *water*, adjusted to pH 2.5 with *dilute orthophosphoric acid*,

  B. a mixture of 5 volumes of *2-propanol* and 95 volumes of *methanol*,
- a gradient programme using the conditions given below,
- 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)	Flow rate (ml per min.)
0	100	0	0.6
8	100	0	0.6
9	98	2	2.2
24	98	2	2.2
50	65	35	1.5
55	25	75	1.5
60	25	75	1.5
61	100	0	1.5
65	100	0	1.5
66	100	0	0.6
70	100	0	0.6

Name	Relative retention time
Cyanoguanidine*	0.32
Metformin	1.00

*Process impurity included for identification only, not to be included in the calculation of total degradation products.

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 10000 theoretical plates and the tailing factor is not more than 1.5 and 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 (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 0.5 times the area of the

principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore the peaks due to dapagliflozin and dapagliflozin related impurities. [*Note- All the impurities related to metformin hydrochloride elute upto 55 minutes. After 55 minutes only impurities related to dapagliflozin are eluted*]

Uniformity of Dosage units (2.5.4). Comply with the tests stated under Tablets.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

For Dapagliflozin —

Buffer solution. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*.

Test solution. Transfer sufficient quantity of intact tablets containing 100 mg of Dapagliflozin to a 500-ml volumetric flask, add 50 ml of the buffer solution, stir on magnetic stirrer for 10 minutes. Add 300 ml of *methanol*, stir on magnetic stirrer for 120 minutes, and allow to stand for 18 to 20 hours. Further stir for 30 minutes and dilute to volume with *methanol*. Centrifuge a portion of the solution at 10000 rpm for 10 minutes. Dilute 2.0 ml of supernatant liquid to 50.0 ml with the buffer solution, filter. *[Note—Stirring time can be increased to ensure complete dispersion of tablets]*.

Reference solution. Dissolve 50 mg of *dapagliflozin IPRS* in 20 ml of *methanol* with the aid of ultrasound. Add 50 ml of the buffer solution and further sonicate for 2 minutes and dilute to 100.0 ml with the buffer solution. Dilute 4.0 ml of the solution to 250.0 ml with the buffer solution.

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),
- column temperature: 30º,
- sample temperature: 5°,
- mobile phase: a mixture of 65 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 35 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 4000 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.

For Metformin Hydrochloride —

Buffer solution. Dissolve 6.8 g of *potassium dihydrogen orthophosphate* and 0.9 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute orthophosphoric acid* or *sodium hydroxide solution*.

Test solution. Transfer sufficient quantity of intact tablets containing 5 g of metformin hydrochloride to a 500-ml volumetric flask, add 50 ml of the buffer solution stir on magnetic stirrer for 10 minutes. Add 300 ml of *methanol*, stir for 120 minutes, and allow to stand for 18 to 20 hours. Further stir for 30 minutes and dilute to volume with *methanol*. Centrifuge a portion of the solution at 10000 rpm for 10 minutes. Dilute 4.0 ml of supernatant liquid to 50.0 ml with the buffer solution. Dilute 3.0 ml of the solution to 50.0 ml with the buffer solution, filter. *[Note— Stirring time can be increased to ensure complete dispersion of tablets]*.

Reference solution. A 0.005 per cent w/v solution of *metformin hydrochloride IPRS* in the buffer 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),
- column temperature: 30º,

– sample temperature: 25°,
– mobile phase: a mixture of 95 volumes of a buffer solution prepared by 0.935 g of *1-pentanesulphonic acid sodium salt monohydrate* in 1000 ml of *water*, adjusted to pH 3.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution* and 5 volumes of *acetonitrile*,
– flow rate: 1.5 ml per minute,
– spectrophotometer set at 233 nm,
– injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 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 $C_4H_{11}N_5$, HCl in the tablet.

Storage. Store at a temperature not exceeding 30º.
