Amlodipine and Olmesartan Medoxomil Tablets

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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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Amlodipine and Olmesartan Medoxomil Tablets

Amlodipine Besylate and Olmesartan Medoxomil Tablets; Amlodipine Besilate and Olmesartan Medoxomil Tablets

Amlodipine and Olmesartan Medoxomil Tablets contain amlodipine besylate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of amlodipine, $C_{20}H_{25}ClN_2O_5$ and olmesartan medoxomil, $C_{29}H_{30}N_6O_6$.

Usual strengths. Amlodipine, 5 mg and Olmesartan Medoxomil, 20 mg; Amlodipine, 5 mg and Olmesartan Medoxomil, 40 mg; Amlodipine, 10 mg and Olmesartan Medoxomil, 20 mg; Amlodipine, 10 mg and Olmesartan Medoxomil, 40 mg.

Identification

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

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 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 *0.2 M sodium hydroxide*,
Speed and time. 50 rpm and 30 minutes (for amlodipine) and 45 minutes (for olmesartan medoxomil).

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 (a). A 0.016 per cent w/v solution of *amlodipine besylate IPRS* in the mobile phase.

Reference solution (b). A 0.044 per cent w/v solution of *olmesartan medoxomil IPRS* in the mobile phase.

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 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- sample temperature: 5°,
- mobile phase: a mixture of 60 volumes of a buffer solution prepared by dissolving 4.08 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.5 with *orthophosphoric acid* and 40 volumes of *acetonitrile*,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Inject reference solution (c). 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 2.0 per cent for both the peaks.

Inject reference solution (c) and the test solution. Run the chromatogram 1.4 times the retention time of the olmesartan medoxomil peak.

Calculate the content of $C_{20}H_{25}ClN_2O_5$ and $C_{29}H_{30}N_6O_6$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{20}H_{25}ClN_2O_5$ and not less than 70 per cent of the stated amount of $C_{29}H_{30}N_6O_6$.

Related substances. Determine by liquid chromatography (2.4.14).

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

Test solution (a). [For tablets strength, amlodipine/olmesartan medoxomil (mg/mg), 5/20] Transfer 5 intact tablets to a 50-ml volumetric flask. Add 10 ml of *water* and sonicate for 5 minutes. Add 10 ml of *acetonitrile* and again sonicate for 5 minutes. Add 15 ml of the solvent mixture and further sonicate for 15 minutes, dilute to volume with the solvent mixture. Centrifuge a portion of the solution for 10 minutes and filter.

Test solution (b). [For tablets strength, amlodipine/olmesartan medoxomil (mg/mg), (5/40, 10/20, 10/40)] Transfer 5 intact tablets to a 100-ml volumetric flask. Add 10 ml of *water* and sonicate for 5 minutes. Add 10 ml of *acetonitrile* and again sonicate for 5 minutes. Add 15 ml of the solvent mixture and further sonicate for 15 minutes, dilute to volume with the solvent mixture. Centrifuge a portion of the solution for 10 minutes and filter.

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

Test solution (d). Dilute 2.0 ml of test solution (b) to 25.0 ml with the solvent mixture.

Reference solution (a). A 0.28 per cent w/v solution of *amlodipine besylate IPRS* in the solvent mixture.

Reference solution (b). A 0.8 per cent w/v solution of *olmesartan medoxomil IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) and 1.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

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

Reference solution (e). A0.005 per cent w/v solution of *amlodipine- impurity D IPRS* in the solvent mixture.

Reference solution (f). Dilute 1.0 ml of reference solution (c) and 10.0 ml of reference solution (e) to 200.0 ml with the solvent mixture.

Reference solution (g). Dilute 2.0 ml of reference solution (f) to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with phenyl group bonded to porous silica (5 µm),
- sample temperature 5°,
- column temperature: 60°,
- mobile phase: A. a buffer solution prepared by dissolving 6.9 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.5 with *orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	68	32
12	68	32
15	30	70
21	30	70
23	68	32
25	68	32

Table-1

Name	Relative retention time	Acceptance criteria Not more than (per cent)
Benzenesulfonic acid[1]	0.13	---
Olmesartan[2]	0.25	2.0
Amlodipine impurity D[3]	0.36	0.5
Amlodipine	0.47	---
Olmesartan medoxomil	1.0	---
Olmesartan medoxomil related compound A[4*]	1.13	---
Olmesartan olefinic impurity[5*]	1.5	---
Olmesartan N-alkyl impurity[6*]	2.03	---
Any other amlodipine or olmesartan medoxomil related impurity	---	0.2
Total impurity (excluding olmesartan)	---	2.0

[1]This peak is due to the counterion and is not to be reported or included in the total impurities,
[*]Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product,
[2]1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylic acid,
[3]3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate],
[4]1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1*H*-furo[3,4-d]imidazol-6(4*H*)-one,
[5](5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1*H*-imidazole-5-carboxylate,
[6](5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2′-(2-trityl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-imidazole-5-carboxylate,
Note- The relative retention times for unspecified amlodipine related impurities are up to 1.0. The relative retention times for unspecified olmesartan medoxomil related impurities are after 1.0 and also at 0.45, 0.60, 0.76, 0.79, and 0.92.

Inject reference solution (f) and (g). The test is not valid unless the tailing factor is not more than 2.0, the relative standard deviation for replicate injections is not more than 5.0 per cent, for amlodipine impurity D, amlodipine and olmesartan medoxomil peaks in the chromatogram obtained with reference solution (f) and the signal-to-noise ratio is not less than 10 for amlodipine impurity D, amlodipine and olmesartan medoxomil peaks in the chromatogram obtained with reference solution (g).

Inject reference solution (f) and test solution (a) (for tablets strength, amlodipine/olmesartan medoxomil (mg/mg), 5/20) or test solution (b) [for tablets strength, amlodipine/olmesartan medoxomil (mg/mg), (5/40, 10/20, 10/40)]

Calculate the percentage of amlodipine impurity D free base in the portion of tablets taken;

$$\text{Amlodipine impurity D} = \frac{At_1}{As_1} \times \frac{Cs_1}{Ct_1} \times \frac{Ma_1}{Ma_2} \times 100$$

Where,
At_1= peak response of amlodipine impurity D from test solution (a) or (b),
As_1= peak response of amlodipine impurity D IPRS from reference solution (f),
Cs_1 = concentration of amlodipine impurity D IPRS in reference solution (f) (mg/ml),
Ct_1 = nominal concentration of amlodipine in test solution (a) or (b) (mg/ml),
Ma_1 = molecular weight of amlodipine impurity D free base 406.86,
Ma_2= molecular weight of amlodipine impurity D 522.94,

Calculate the percentage of any unspecified amlodipine related impurity in the portion of Tablets taken:

$$\text{Unspecified Amlodipine impurity D} = \frac{At_2}{As_2} \times \frac{Cs_2}{Ct_2} \times \frac{Mb_2}{Mb_2} \times 100$$

Where,
At_2= peak response of any other amlodipine related impurity from test solution (a) or (b),
As_2= peak response of amlodipine from reference solution (d),
Cs_2= concentration of amlodipine besylate IPRS in reference solution (d) (mg/ml),
Ct_2= nominal concentration of amlodipine in test solution (a) or (b) (mg/ml),
Mb_1= molecular weight of amlodipine, 408.88,
Mb_2= molecular weight of amlodipine besylate, 567.05,

Calculate the percentage of olmesartan or any other olmesartan medoxomil related impurity in the portion of Tablets taken:

$$\text{Result} = \frac{At_3}{As_3} \times \frac{Cs_3}{Ct_3} \times 100$$

Where,
At_3= peak response of olmesartan or any other olmesartan medoxomil related impurity from test solution (a) or (b),
As_3= peak response of olmesartan medoxomil from reference solution (f),
Cs_3= concentration of olmesartan medoxomil IPRS in reference solution (f) (mg/ml),
Ct_3= nominal concentration of olmesartan medoxomil in test solution (a) or (b) (mg/ml),

Acceptance criteria: see Table-1

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

Determine by liquid chromatography (2.4.14), as described under Related substances with the following modification.

Test solution. Disperse 1 intact tablet in 10 ml of *water* with the aid of ultrasound for 5 minutes, add 10 ml of *acetonitrile* and again sonicate for 5 minutes. Add 15 ml of the solvent mixture and further sonicate for 15 minutes, and dilute to 50.0 ml with the solvent mixture to obtain a solution having similar concentration to the reference solution.

Reference solution. A 0.014 per cent w/v solution of *amlodipine besylate IPRS* in the solvent mixture.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{25}ClN_2O_5$ in the tablet.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14). as described under Related substances with the following modifications.

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

Inject reference solution (d) and test solution (c) [for tablets strength, amlodipine/olmesartan medoxomil (mg/mg), 5/20] or test solution (d) [for tablets strength, amlodipine/olmesartan medoxomil (mg/mg), (5/40, 10/20, 10/40)].

Calculate the content of $C_{20}H_{25}ClN_2O_5$ and $C_{29}H_{30}N_6O_6$in the tablets.

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

Labelling. The label states the quantity of amlodipine besylate in the term of the equivalent amount of amlodipine and olmesartan medoxomil.