Amlodipine and Valsartan Tablets

Amlodipine Besylate and Valsartan Tablets; Amlodipine Besilate and Valsartan Tablets.

Amlodipine and Valsartan 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 valsartan, $C_{24}H_{29}N_5O_3$.

Usual strengths. Amlodipine, 5 mg and Valsartan, 80 mg; Amlodipine, 5 mg and Valsartan, 160 mg; Amlodipine, 10 mg and Valsartan, 160 mg.

Identification

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

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 1000 ml of a buffer solution prepared by dissolving 6.81 g of *monobasic potassium phosphate* and 0.9 g of *sodium hydroxide* in *water* and dilute to 1000 ml with *water*, adjusted to pH 6.8 with *0.2 M sodium hydroxide* or *1M orthophosphoric acid,*
Speed and time. 75 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).
Solvent mixture. A 0.1 per cent w/v solution of *polysorbate 80* in the dissolution medium.

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

Reference solution (a). Dissolve 40 mg, each of *amlodipine besylate IPRS* and *valsartan IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with the dissolution medium.

Reference solution (b). Dissolve 72 mg of *amlodipine besylate IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A 0.16 per cent w/v solution of *valsartan IPRS* in *methanol.*

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

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with phenyl group bonded to porous silica (4 µm) (Such as Synergi Polar-RP),
- column temperature: 40º,
- mobile phase: a mixture of 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.2 volume *trifluoroacetic acid*,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Inject reference solution (a) and (d). The test is not valid unless the resolution between the peaks due to amlodipine and valsartan is not less than 2.0 in the chromatogram obtained with reference solution (a), 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 in the chromatogram obtained with reference solution (d).

Inject reference solution (d) and the test solution.

Calculate the content of $C_{20}H_{25}C1N_2O_5$and $C_{24}H_{29}N_5O_3$in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{20}H_{25}C1N_2O_5$ and $C_{24}H_{29}N_5O_3$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of mobile phase A and mobile phase B.

Test solution (a). Disperse a quantity of intact tablets containing 50 mg of amlodipine in 50 ml of *water,* with the aid of ultrasound, add 350 ml of the solvent mixture and shake for 45 minutes. Sonicate for 15 minutes with intermittent shaking, dilute with the solvent mixture to obtain 0.02 per cent w/v of amlodipine. Centrifuge the solution for about 10 minutes at 3000 rpm. Use the clear supernatant.

Test solution (b). Dilute a suitable volume of test solution (a) to 100.0 ml with the solvent mixture to obtain a solution containing 0.016 per cent w/v of valsartan.

Reference solution (a). Dissolve 70 mg of *amlodipine besylate IPRS* and 80 mg of *valsartan IPRS* in 2.5 ml *methanol* and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (b). A 0.008 per cent w/v solution of *valsartan related compound B IPRS* in reference solution (a).

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (d). A solution containing 0.005 per cent w/v of *amlodipine related compound A IPRS* (as free base) and 0.003 per cent w/v, each of, *amlodipine besylate IPRS* and *valsartan IPRS,* prepared by dissolving in *methanol* (5 per cent of the final volume) and dilute to volume with the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- sample temperature: 10°
- mobile phase: A. a 1 per cent v/v solution of *triethylamine* in *water,* adjusted to pH 2.8 with *orthophosphoric acid,*

  B. a mixture of 70 volumes of *methanol* and 30 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 237 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase A (per cent v/v)
0	50	50
3	50	50
15	30	70
20	30	70
20.1	50	50
25	50	50

Name	Relative retention time
Devaleryl valsartan[1]	0.24
Amlodipine related compound A[2]	0.50
Valsartan related degradation product 1[3]	0.54
Valsartan related degradation product 2[3]	0.81
Amlodipine	1.00
Valsartan related compound B[4]	1.34
Valsartan related degradation product 3[3]	1.44
Valsartan	1.74
Valsartan related degradation product 4[3]	2.06
Valsartan ethyl ester[5]	2.32

[1]N-{[2′-(1H-Tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine,
[2]3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate],
[3]These are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities,
[4]N-Butyryl-N-{[2′-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine,
[5]N-Valeryl-N-{[2′-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine ethyl ester.

Inject reference solution (b), (c) and (d).The test is not valid unless the resolution between the peaks due to amlodipine and valsartan related compound B and between the peaks due to valsartan related compound B and valsartan is not less than 4.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for amlodipine related compound A, amlodipine and valsartan peaks is not more than 5.0 per cent in the chromatogram obtained with reference solution (d) and the signal-to- noise ratio for amlodipine and valsartan peaks is not less than 10.0 in the chromatogram obtained with reference solution (c).

Inject reference solution (d), test solution (a) and (b). In the chromatogram obtained with test solution (b), the area of any peak corresponding to devaleryl valsartan, valsartan related degradation product 1, valsartan related degradation product 2, valsartan related degradation product 3, valsartan related degradation product 4 and valsartan ethyl ester, each of, is not more than the area of the valsartan peak in the chromatogram obtained with reference solution (d) (0.2 per cent). In the chromatogram obtained with test solution (a), the area of any peak corresponding to amlodipine related compound A (free base) is not more than 1.25 times the area of amlodipine related compound A peak in the chromatogram obtained with reference solution (d) (0.5 per cent), the area of any other secondary peak is not more than the area of amlodipine peak in the chromatogram obtained with reference solution (d) (0.2 per cent). The sum of all the impurities is not more than 1.2 per cent. If valsartan related compound A is a potential degradation product. Than sum of all the impurities other than valsartan related compound A and amlodipine related compound A is not more than 2.0 per cent. Ignore the peaks due to valsartan related compound B, benzene sulphonic acid at relative retention time about 0.19 and any peak with an area less than 0.5 times the area of the amlodipine peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

Limit of valsartan related compound A. Determine by liquid chromatography (2.4.14).
NOTE- Valsartan related compound A is a process impurity and a formulation-specific degradation product.

Test solution. Disperse a quantity of the powdered tablets containing 50 mg of Valsartan in the mobile phase with the aid of ultrasound and dilute to 100.0 ml with the mobile phase.

Reference solution (a). A 0.004 per cent w/v solution, each of *valsartan related compound A IPRS* and *valsartan IPRS* in the mobile phase.

Reference solution (b). A 0.0001 per cent w/v solution of *valsartan related compound A IPRS (N*-Valeryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-D-valine*)* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with cellulose tris-(3,5-dichlorophenyl carbamate bonded to porous silica (5 µm) (Such as Chiracel OD-H),
- sample temperature: 10°
- mobile phase: a mixture of 85 volumes of *n-hexane,* 15 volumes of *2-propanol* and 0.1volume of *trifluoroacetic acid,*
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 20 µl,

The relative retention time with reference to valsartan for valsartan related compound A is about 0.7.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to valsartan and valsartan related compound A is not less than 2.0 in the chromatogram obtained with reference solution (a) and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. Run the chromatogram 3.5 times the retention time of valsartan related compound A for test solution. The area of any secondary peak corresponding to valsartan related compound A is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent).

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 modifications.

Test solution. Disperse 1 tablet in *water* (10 per cent of the final volumes) with the aid of ultrasound with intermittent shaking, dilute with the solvent mixture to obtain a solution containing 0.01 per cent w/v of Amlodipine.

Reference solution. A 0.014 per cent w/v solution of *amlodipine besylate IPRS,* prepared by adding *methanol* (upto 5 per cent of the final volume) to dissolve and dilute to volume with the solvent mixture.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{25}C1N_2O_5$ 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.

Inject reference solution (a). 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 amlodipine and valsartan peaks.

Inject reference solution (a) and test solution (a) and (b).

Calculate the content of $C_{20}H_{25}C1N_2O_5$ in test solution (a) and $C_{24}H_{29}N_5O_3$in test solution (b) in the tablets.

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

Labelling. The label states the strength in terms of the equivalent amount of amlodipine and valsartan.