Amantadine 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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Amantadine Tablets

Amantadine Hydrochloride Tablets

Amantadine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of amantadine hydrochloride, $C_{10}H_{17}N,HCl$.

Usual strengths. 100 mg.

Identification

A. Weigh a quantity of powder containing 0.2 g of amantadine hydrochloride in to a suitable beaker. Add 20 ml of *0.1 M hydrochloric acid*, sonicate for 5 minutes, filter. Transfer the filtrate to a separatory funnel, add 1 ml of *5 M sodium hydroxide*, and shake. Add 5 ml of *methylene chloride* to the solution, shake, and allow the two layers to separate for about 20 minutes. Pass the lower layer through *sodium sulphate anhydrous*, then rinse the sodium sulphate with 2 ml of *methylene chloride*. Evaporate the filtrate under nitrogen. The dried residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *amantadine hydrochloride IPRS*, treated in the same manner or with the reference spectrum of amantadine.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution.

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 500 ml of *water*,
Speed and time. 50 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.012 per cent v/v solution of *naphthalene* in *toluene*.

Test solution. Transfer 5.0 ml of filtrate to a separatory funnel, add 2.5 ml of *5 M sodium hydroxide* and 5 ml of the internal standard solution and shake well, for 10 minutes. Allow the two layers to separate and use the clear upper layer.

Reference solution. A 0.02 per cent w/v solution of *amantadine hydrochloride IPRS* in the dissolution medium. Transfer 5.0 ml of the solution to a separatory funnel, add 2.5 ml of *5 M sodium hydroxide* and 5 ml of internal standard solution and shake well, for 10 minutes. Allow the two layers to separate and use the clear upper layer.

Chromatographic system
- a fused silica capillary column 30 m x 0.32 mm, packed with 5 per cent Phenyl- 95 per cent methylpolysiloxane (film thickness 1.0 µm) (Such as Rtx-5 Amine),
- temperature:
  column 120° for 1 minutes, 120° to 240° @ 25° per minute and hold at 240° for 2 minutes,
- inlet port at 280º and detector at 300º,
- flame ionization detector,
- split ratio: 50:1,
- flow rate: 1.5 ml per minute using nitrogen as carrier gas.

– injection volume: 2 µl,

The relative retention time with reference to amantadine, for naphthalene is about 0.94.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to naphthalene (internal standard) and amantadine is not less than 5.0 and the relative standard deviation of the ratio of peak area of amantadine to that of peak area of the naphthalene (internal standard), for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of amantadine hydrochloride using ratio of the peak area of amantadine hydrochloride to that of peak area of the (naphthalene) internal standard.

Calculate the content of $C_{10}H_{17}N$,HCl in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{10}H_{17}N$,HCl.

Related substances. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.05 per cent v/v solution of *adamantane* in *toluene*.

Test solution. Transfer a quantity of powdered tablets containing 0.5 g of Amantadine hydrochloride to a suitable container and add 20 ml of *5 M sodium hydroxide* and disperse with the aid of ultrasound for 15 minutes with intermittent shaking. Add 10.0 ml of internal standard solution and further sonicate for 15 minutes with intermittent shaking. Centrifuge the solution at 3000 rpm for 10 minutes. Transfer 3.0 ml of supernatant to a test tube, add 300 mg of *sodium sulphate anhydrous* to remove traces of water. Allow the sodium sulphate to precipitate and use the clear solution.

Reference solution. Transfer 50 mg of *amantadine hydrochloride IPRS* to a suitable container, add 20 ml of *5 M sodium hydroxide* and dissolve with the aid of ultrasound for 15 minutes with intermittent shaking. Add 10.0 ml of the internal standard solution and further sonicate for 15 minutes with intermittent shaking. Centrifuge the solution at 3000 rpm for 10 minutes. Transfer 3.0 ml of supernatant to a test tube, add 300 mg of *sodium sulphate anhydrous* to remove traces of water. Allow the sodium sulphate to precipitate. Dilute 1.0 ml of the clear solution to 10.0 ml with internal standard solution.

Chromatographic system
– a fused silica capillary column 30 m x 0.53 mm, packed with 5 per cent Phenyl- 95 per cent methylpolysiloxane (film thickness 1.0 µm) (Such as Rtx-5 Amine),
– temperature:
  column 70° for 5 minutes, 70° to 250° @ 10° per minute and hold at 250° for 17 minutes,
– inlet port at 220º and detector at 300º,
– flame ionization detector,
– split ratio: 50:1,
– flow rate: 4 ml per minute using helium as carrier gas.
– injection volume: 1 µl,

The relative retention time with reference to amantadine, for adamantane is about 0.83.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to adamantane (internal standard) and amantadine is not less than 20.0 and relative standard deviation of the ratio of peak area of amantadine to that of peak area of the adamantane (internal standard) 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 0.2 times the area of the principal peak in the chromatogram obtained with the reference solution (0.2 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 the reference solution (0.5 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.10 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by gas chromatography (2.4.13).

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

Internal standard solution. A 0.05 per cent v/v solution of *naphthalene* in *toluene*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing 1 g of Amantadine in 200 ml of the solvent mixture with the aid of ultrasound for 30 minutes with intermittent shaking and dilute to 250.0 ml with the solvent mixture. Centrifuge a portion of the solution at 3000 rpm for 10 minutes. Transfer 1.0 ml of supernatant to a test tube, add 5 ml of *5 M sodium hydroxide* and 5.0 ml of internal standard solution. Shake for 10 minutes allow to separate the two layers and collect 4 ml of the clear upper layer, add 500 mg of *sodium sulphate anhydrous* to remove traces of water. Use the clear solution.

Reference solution. Dissolve 40 mg of *amantadine hydrochloride IPRS* in 4 ml of solvent mixture, with the aid of ultrasound 5 minutes and dilute to 10.0 ml with the solvent mixture. Transfer 1.0 ml of the solution to a test tube, add 5 ml of *5 M sodium hydroxide* and 5.0 ml of internal standard solution. Shake for 10 minutes allow to separate the two layers and collect 4 ml of the clear upper layer, add 500 mg of *sodium sulphate anhydrous* to remove traces of water. Use the clear solution.

Chromatographic system
- a fused silica capillary column 30 m x 0.32 mm, packed with 5 per cent Phenyl- 95 per cent methylpolysiloxane (film thickness 1.0 µm) (Such as Rtx-5 Amine),
- temperature:
  column 120° for 2 minutes, 120° to 270° @ 30° per minute and hold at 270° for 5 minutes,
- inlet port at 280º and detector at 300º,
- flame ionization detector,
- split ratio: 80:1,
- flow rate: 2 ml per minute using nitrogen as carrier gas.
- injection volume: 2 µl,

The relative retention time with reference to amantadine, for naphthalene (internal standard) is about 0.94.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to naphthalene (internal standard) and amantadine is not less than 5.0, the tailing factor is not more than 1.2 and the relative standard deviation of the ratio of peak area of amantadine to that of peak area of the naphthalene (internal standard), for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{10}H_{17}N,HCl$ in the tablets. Using ratio of the peak area of amantadine to that of peak area of naphthalene (internal standard).

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