

Government of Nepal
Ministry of Health and Population
Department of Drug Administration
National Medicines Laboratory
Quality and Method Validation Section
Memantine HCl & Donepezil HCl Tablets

Analytical Profile No.: Meman Donep 079/080/AP 122

Memantine HCl & Donepezil HCl Tablets contains not less than 90.0% and not more than 110.0% of the stated amount of Memantine HCl & Donepezil HCl.

Usual Strength: 5 mg & 10 mg

1. Identification:

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

2. Dissolution: *Determine by liquid chromatography*

2.1 For Memantine HCl

2.1.1 Dissolution Parameters:

Apparatus: Basket

Medium: 900 ml of Simulated gastric fluid pH 1.2

Speed and Time: 100 rpm and 45 minutes

Withdraw a suitable volume of the medium and centrifuge to get a clear supernatant solution.

2.1.2 Simulated gastric fluid pH 1.2: Dissolve 2 gm of sodium chloride and 7 ml of concentrated HCl in 1000 ml of water and adjust pH to 1.2 ± 0.1 with dilute HCl or dilute NaOH.

2.1.3 Diluent: Mix Water and acetonitrile in the ratio 30:70.

2.1.4 Reagent 1: Dilute 10ml of triethylamine to 100ml with acetonitrile.

2.1.5 Reagent 2: Prepare 1% w/v of F-MOC reagent in acetonitrile. [Use this reagent freshly only]

2.1.6 Test Solution: Pipette out 5ml of clear supernatant solution in 25 ml of volumetric flask, derivatize the solution as per derivatization method given.

2.1.7 Reference Solution: Weigh accurately and transfer about 30 mg of Memantine hydrochloride WS to a 100 ml volumetric flask (amber color); add about 70 ml of dissolution media, sonicate to dissolve, cool to room temperature and make up the volume with same solvent. Dilute 2 ml of this solution to 100ml with the dissolution media. Transfer 5 ml of this solution in a 25 ml volumetric flask and derivatize as per derivatization method given.

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2.1.8 Derivatization Method: To 5ml of solution in a 25 ml volumetric flask, add 1 ml of Reagent-1 and vortex for 5 minutes. Further add 5 ml of Reagent-2 and again vortex for 5 minutes. Heat this solution in water bath at 60° C for 10 minutes, cool and make up the volume with diluent.

2.1.9 Chromatographic system:

Column: Luna C-8, 4.6mm X 250-mm, 5 μ (Phenomenex)

Flow rate: 1.5 ml/min

Wavelength: 263 nm

Injection volume: 100 μ l

Column oven Temperature: Ambient

Sample cooler Temperature: 4°C

Mobile Phase: A mixture of 20 volume of Buffer and 80 volume of Acetonitrile and adjust the pH to 3.0 \pm 0.05 with triethylamine.

Buffer: Add 1 ml trifluoroacetic acid in 1000ml water.

2.1.10 Procedure: Inject the derivatized reference solution and the test solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%. Measure the peak responses. Calculate the percent release of Memantine HCl.

2.1.11 Limit: Not less than 70 percent (D) of the stated amount of Memantine HCl.

2.2 For Donepezil HCl

2.2.1 Dissolution Parameters:

Apparatus: Basket

Medium: 900 ml of Simulated gastric fluid pH 1.2

Speed and Time: 100 rpm and 45 minutes

Withdraw a suitable volume of the medium and centrifuge to get a clear supernatant solution.

2.2.2 Simulated gastric fluid pH 1.2: Dissolve 2 gm. of sodium chloride and 7 ml of concentrated HCl in 1000 ml of water and adjust pH to 1.2 with dilute HCL or NaOH.

2.2.3 Test Solution: Use the filtrate

2.2.4 Reference Solution: Weigh accurately about 30 mg of Donepezil Hydrochloride WS in 100 ml of volumetric flask; add about 70 ml of dissolution media, sonicate to dissolve, cool to

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room temperature and make up the volume with same solvent. Dilute 2ml of this solution to 100 ml with dissolution media and mix.

2.2.5 Chromatographic system:

Column: Inertsil C-8, 4.6mm X 250-mm, 5 μ

Flow rate: 1.0 ml/min

Wavelength: 271 nm

Injection volume: 100 μ l

Column oven Temperature: 50°C

Sample cooler Temperature: Ambient

Mobile Phase: A mixture of 550 volume of Buffer, 450 volume of Methanol and 5 volume of Triethylamine. Adjust the pH to 2.50 ± 0.05 with Orthophosphoric acid.

Buffer: Dissolve 2.73 gm of potassium dihydrogen orthophosphate in 1000 ml of water.

2.2.6 Procedure: Inject the derivatized reference solution and the test solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%. Measure the peak responses. Calculate the percent release of Donepezil HCl.

2.2.7 Limit: Not less than 70 percent (D) of the stated amount of Donepezil HCl.

3. Uniformity of Content

3.1 For Memantine HCl

Determine by liquid chromatography, as described in the Assay for Memantine HCl, using the following test solution.

Test Solution: Put 1 table in 50 ml volumetric flask, dissolve with diluent and make up the volume. Further take 5 ml of this solution in a 25 ml volumetric flask, to it add 1 ml of Reagent-1 and shake it vigorously. To this add 5 ml of Reagent-2. Heat the content in water bath at 60° C for 10 minutes, cool and make up the volume with diluent.

3.2 For Donepezil HCl

Determine by liquid chromatography, as described in the Assay for Donepezil HCl, using the following test solution.

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Test Solution: Place 1 tablet in 50 ml of volumetric flask and dissolve and makeup the volume with mobile phase.

4. Assay: *Determine by liquid chromatography*

4.1 For Memantine HCl

4.1.2 Diluent: Mix Water and acetonitrile in the ratio 30:70.

4.1.3 Reagent 1: Dilute 10ml of triethylamine to 100ml with acetonitrile.

4.1.4 Reagent 2: Prepare 1% w/v of F-MOC reagent in acetonitrile. [Use this reagent freshly only]

4.1.5 Test solution: Weigh and powder 20 tablets. Transfer the tablets powder equivalent to 10 mg of memantine hydrochloride into 100 ml volumetric flask, add 70 ml of diluent and sonicate, cool to room temperature. Make up the volume with diluent, mix and centrifuge at 5000 RPM for 10 minutes. Further take 5 ml of this clear solution into 25 ml volumetric flask, to it add 1 ml of Reagent-1 and shake it vigorously. To this add 5 ml of Reagent-2. Heat the content in water bath at 60° C for 10 minutes, cool and make up the volume with diluent.

4.1.6 Reference solution: Weigh accurately and transfer about 25 mg of Memantine hydrochloride WS to a 50 ml volumetric flask (amber color); add about 35 ml of diluent and sonicate to dissolve. Make up the volume with same solvent. Dilute 5 ml of this solution to 25ml with diluent. Further take 5 ml of this solution in a 25 ml volumetric flask, to it add 1 ml of Reagent-1 and shake it vigorously. To this add 5 ml of Reagent-2. Heat the content in water bath at 60° C for 10 minutes, cool and make up the volume with diluent.

4.1.7 Chromatographic system:

Column: Luna C-8, 4.6mmX 250mm, 5μ (Phenomenex)

Flow rate: 1.5 ml/min

Wavelength: 263 nm

Injection volume: 50μl

Column oven Temperature: Ambient

Sample cooler Temperature: 4°C

Mobile Phase: A mixture of 20 volume of Buffer and 80 volume of Acetonitrile and adjust the pH to 3.0 ± 0.05 with triethylamine.

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Buffer: Add 1 ml trifluoroacetic acid in 1000ml water.

4.1.8 Procedure: Inject the reference solution five times and sample solutions. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%. Measure the peak responses. Calculate the content of Memantine HCl in Memantine HCl & Donepezil HCl Tablets.

4.2 For Donepezil HCl

4.2.1 Test solution: Weigh and powder 20 tablets. Transfer the tablets powder equivalent to 10 mg of donepezil hydrochloride into 100 ml volumetric flask, add 70 ml of mobile phase and sonicate, cool to room temperature. Make up the volume with mobile phase, mix and centrifuge at 3000 RPM for 10 minutes.

4.2.2 Reference solution: Weigh accurately about 50 mg of Donepezil Hydrochloride WS in 100 ml of volumetric flask; add about 70ml of mobile phase and sonicate to dissolve. Cool and make up the volume with same solvent. Dilute 5ml of this solution to 25 ml with mobile phase.

4.2.3 Chromatographic system:

Column: Inertsil C-8, 4.6mmX 250-mm, 5 μ

Flow rate: 1.0 ml/min

Wavelength: 271 nm

Injection volume: 20 μ l

Column oven Temperature: 50°C

Mobile Phase: A mixture of 550 volume of Buffer, 450 volume of Methanol and 5 volume of Triethylamine. Adjust the pH to 2.50 ± 0.05 with Orthophosphoric acid.

Buffer: Dissolve 2.73 gm of potassium dihydrogen orthophosphate in 1000 ml of water.

4.2.4 Procedure: Inject the reference solution five times and sample solutions. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%. Measure the peak responses. Calculate the content of Donepezil HCl in Memantine HCl & Donepezil HCl Tablets.

5. Other tests: As per pharmacopoeial requirements.