Paracetamol and Mefenamic Acid 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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Paracetamol and Mefenamic Acid Tablets

Acetaminophen and Mefenamic Acid Tablets

Paracetamol and Mefenamic Acid Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of paracetamol, $C_8H_9NO_2$ and mefenamic acid, $C_{15}H_{15}NO_2$.

Usual strengths. Paracetamol 325 mg and Mefenamic acid 500 mg; Paracetamol 450 mg and Mefenamic acid 500 mg; Paracetamol 500 mg and Mefenamic acid 250 mg.

Identification

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

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium. 900 ml of tris buffer pH 9.0, prepared by dissolving 6.08 g of *tris (hydroxymethyl) aminomethane* in 1000 ml of *water*, adjusted to pH 9.0 with *orthophosphoric acid*, add 10 g of *sodium lauryl sulphate*
Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. A 0.04 per cent w/v solution of *sodium hydroxide* in *methanol*.

Test solution. Dilute 5.0 ml of the filtrate to 50.0 ml with the mobile phase.

Reference solution (a). A 0.055 per cent w/v solution of *mefenamic acid IPRS* in the solvent mixture.

Reference solution (b). A 0.050 per cent w/v solution of *paracetamol IPRS* in the solvent mixture.

Reference solution (c). Dilute suitable volume of reference solution (a) and reference solution (b) with the mobile phase to obtain a solution having similar concentration to the test solution.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as Avantor ACE),
- mobile phase: a mixture of 50 volumes of a buffer solution prepared by dissolving 8.37 g of *potassium dihydrogen phosphate* and 6.71 g *dipotassium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution*, 40 volumes of *acetonitrile* and 10 volumes of *methanol*.
- flow rate: 1 ml per minute,
- spectrophotometer set at 285 nm,
- injection volume: 10 µl.

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 1500 theoretical plates, 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.

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Calculate the content of $C_8H_9NO_2$ and $C_{15}H_{15}NO_2$ in the medium.

Q. Not less than 70 per cent of the stated amount of $C_8H_9NO_2$ and $C_{15}H_{15}NO_2$.

Related substances. Determine by liquid chromatography (2.4.14).

For Paracetamol—

NOTE — Use freshly prepared solutions.

Buffer solution. Dissolving 8.37 g of *potassium dihydrogen orthophosphate* and 6.71 g *potassium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution.*

Solvent mixture. Equal volume of the buffer solution and *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 325 mg of Paracetamol in the solvent mixture with the aid of ultrasound for 10 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture, filter.

Reference solution (a). A 0.00163 per cent w/v solution of *4-aminophenol IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.00163 per cent w/v solution of *4-aminophenol IPRS*, 0.00325 per cent w/v of *paracetamol IPRS* and 0.0025 per cent w/v solution of *mefenamic acid IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as Inertsil ODS 3V),
- mobile phase: A. a mixture of 90 volumes of the buffer solution and 10 volumes of *acetonitrile*,
  B. a mixture of 40 volumes of the buffer solution and 60 volumes of *acetonitrile*.
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
12	100	0
12.5	0	100
20	0	100
20.5	100	0
25	100	0

Inject reference solution (b) to identify the peaks due to 4-aminophenol, paracetamol and mefenamic acid.

The elution order is 4-aminophenol, paracetamol and mefenamic acid.

Inject reference solution (a). The test is not valid unless the column efficiency is not less than 1000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to 4-aminophenol is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

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For Mefenamic acid—

Buffer solution. Dissolving 8.37 g of *potassium dihydrogen orthophosphate* and 6.71 g *dipotassium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide solution.*

Solvent mixture. Equal volume of the buffer solution and *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of Mefenamic acid in the solvent mixture with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture, filter.

Reference solution. A 0.0005 per cent w/v solution of *mefenamic acid IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS 3V),
- mobile phase: a mixture of 55 volumes of the buffer solution and 45 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 285 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 1500 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent). Ignore the peaks due to paracetamol and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

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).

NOTE — Use freshly prepared solutions.

Solvent mixture. A 0.04 per cent w/v solution of *sodium hydroxide* in *methanol*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing 125 mg of Mefenamic acid in the solvent mixture with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 250.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution (a). A 0.05 per cent w/v solution of *mefenamic acid IPRS* in the solvent mixture.

Reference solution (b). A 0.045 per cent w/v solution of *paracetamol IPRS* in the solvent mixture.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with the mobile phase to obtain a solution having similar concentration to the test solution.

Use chromatographic system as described under Dissolution.

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The elution order of the peak is paracetamol followed by mefenamic acid peak.

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 1500 theoretical plates, 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.

Calculate the content of $C_8H_9NO_2$ and $C_{15}H_{15}NO_2$ in the tablets.

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

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