Aceclofenac and Paracetamol 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.

Document History and Schedule for the Adoption Process

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Aceclofenac and Paracetamol Tablets

Aceclofenac and Paracetamol Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of aceclofenac, $C_{16}H_{13}C_{12}NO_4$ and paracetamol, $C_8H_9NO_2$.

Usual strength. Aceclofenac 100 mg and Paracetamol 325 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 the reference solution (c).

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium. 900 ml of phosphate buffer pH 6.8, prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 6.8 with *dilute sodium hydroxide*,
Speed and time. 75 rpm and 45 minutes.

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. Dissolve 11 mg of *aceclofenac IPRS* and 36 mg *paracetamol IPRS* in 5 ml of *acetonitrile* and dilute to 100.0 ml with the dissolution medium.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as X-Terra RP 18),
- mobile phase: A. a mixture of 90 volumes of *0.005 M disodium hydrogen phosphate*, adjusted to pH 8.0 with *dilute orthophosphoric acid*, 9 volumes of *acetonitrile* and 1 volume of *methanol*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *methanol*.
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 280 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
10	35	65
11	95	5
15	95	5

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 2.0 per cent, for both the peaks.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{13}C_{12}NO_4$ and $C_8H_9NO_2$ in the medium.

Q. Not less than 70 per cent of the stated amount of $C_{16}H_{13}C_{12}NO_4$ and $C_8H_9NO_2$.

Related substances. Determine by liquid chromatography (2.4.14).

For Aceclofenac—

Solvent mixture. 20 volumes of *acetonitrile* and 80 volumes of *water*.

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of Aceclofenac in 10 ml of *acetonitrile*, with the aid of ultrasound for 5 minutes with intermittent shaking, Add 30 ml of the solvent mixture and sonicate for 15 minutes with intermittent shaking, dilute to 50.0 ml with the solvent mixture, filter.

Reference solution (a). Dissolve 20 mg of *aceclofenac IPRS* in 20 ml of *acetonitrile*, with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution (b). A 0.054 per cent w/v solution of *diclofenac sodium IPRS* (aceclofenac impurity A) [([2-[(2,6-dichlorophenyl)amino] phenyl]acetic acid] in the solvent mixture.

Reference solution (c). Transfer 1.0 ml of *reference solution (a)* and 10.0 ml of *reference solution (b)* to a 50- ml volumetric flask, add 5 ml of *acetonitrile* and dilute to volume with 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 Eclipse XDB 18),
- sample temperature: 8°,
- mobile phase: A. a mixture of 90 volumes of *0.005 M disodium hydrogen phosphate*, adjusted to pH 8.0 with *dilute orthophosphoric acid*, 9 volumes of *acetonitrile* and 1 volume of *methanol*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *methanol*.
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	85	15
30	70	30
40	35	65
50	35	65
51	85	15
60	85	15

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to aceclofenac and aceclofenac impurity A is not less than 5.0, the column efficiency is not less than 2000 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 for both the peaks.

Inject reference solution (c) and the test solution. In the chromatogram obtained with the test solution, the area of peak corresponding to aceclofenac impurity A is not more than twice the area of the peak due to diclofenac (aceclofenac impurity A) in the chromatogram obtained with reference solution (c) (5.0 per cent). The area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.4 per cent) and the sum of the areas of all the secondary peaks other than diclofenac peak (aceclofenac impurity A) is not more than 7.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.5 per cent). Ignore the peaks up to 7 minutes due to paracetamol, 4-aminophenol and any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (c) (0.05 per cent).

For Paracetamol—

NOTE — Use freshly prepared solutions.

Solvent mixture. 90 volumes of *water* and 10 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of Paracetamol in 20 ml of *acetonitrile*, with the aid of ultrasound with intermittent shaking. Add 100 ml of the solvent mixture and sonicate for 15 minutes with intermittent shaking, dilute to 200.0 ml with the solvent mixture, filter.

Reference solution. Dissolve a quantity of containing 25 mg of *paracetamol IPRS* in 10 ml of *acetonitrile*, with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the solvent mixture. Transfer 1.0 ml of the solution to 200-ml volumetric flask, add 20 ml of *acetonitrile* and dilute to volume with 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 Eclipse XDB 18),
- sample temperature: 8°,
- mobile phase: A. a mixture of 90 volumes of a *0.005 M disodium hydrogen phosphate*, adjusted to pH 8.0 with *dilute orthophosphoric acid*, 9 volumes of *acetonitrile* and 1 volume of *methanol*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *methanol*.
- flow rate: 1 ml per minute
- a gradient programme using the conditions given below,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
20	85	15
22	45	55
32	45	55
33	100	0
40	100	0

The relative ~~retemtion~~retention time with paracetamol, for 4-aminophenol is about 0.67

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 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.~~, for both the peaks.~~

Inject the reference solution 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 0.4 times the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent). The area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.25 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent). Ignore the peaks after 20 minutes due to aceclofenac and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with the reference solution ~~(c)~~ (0.05 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions.

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

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing 325 mg of Paracetamol in 40 ml of *acetonitrile*, with the aid of ultrasound with intermittent shaking. Add 100 ml of the solvent mixture and sonicate for 15 minutes with intermittent shaking, dilute to 200.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (a). Dissolve 32.5 mg of *paracetamol IPRS* in 5 ml of *acetonitrile*, with the aid of ultrasound for 5 minutes and dilute to 20.0 ml with the solvent mixture.

Reference solution (b). Dissolve 25 mg of *aceclofenac IPRS* in 10 ml of *acetonitrile*, with the aid of ultrasound for 5 minutes and dilute to 50.0 ml with the solvent mixture.

Reference solution (c). Transfer 5.0 ml, each of, reference solution (a) and reference solution (b) to a 50- ml volumetric flask. Add 10 ml of *acetonitrile* and dilute to 50.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as X-Terra RP 18),
- mobile phase: A. a mixture of 90 volumes of *0.005 M disodium hydrogen phosphate*, adjusted to pH 8.0 with *dilute orthophosphoric acid*, 9 volumes of *acetonitrile* and 1 volume of *methanol*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *methanol*.
- flow rate: 1 ml per minute
- a gradient programme using the conditions given below,
- spectrophotometer set at 280 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
10	35	65
11	95	5
15	95	5

The elution order is paracetamol followed by aceclofenac peak.

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 2000 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, for both the peaks.

Inject reference solution (c) and test solution.

Calculate the content of $C_{16}H_{13}C_{12}NO_4$ and $C_8H_9NO_2$ in the tablets.

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