Adapalene Gel

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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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Adapalene Gel

Adapalene Gel contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of adapalene, $C_{28}H_{28}O_3$.

Usual strength. 0.1 per cent w/w

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel F254* (Such as Merck silica gel 60 RP-18 *F254* plates).

Mobile phase. A mixture of 18 volumes of *stabiliser-free tetrahydrofuran* and 82 volumes of *methanol*.

Test solution. Transfer a quantity of gel containing 5 mg of Adapalene, add 10 ml of *stabiliser-free tetrahydrofuran* and shake to disperse. Add *methanol* to produce a solution containing 0.025 per cent w/v of Adapalene and filter through 0.2 µm Dynagard PP filter.

Reference solution. A 0.025 per cent w/v solution of *adapalene IPRS* in the mobile phase.

Apply to the plate 1 µl of each solution. Allow the mobile phase to rise 15 cm. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatograms obtained with the reference solution.

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

Tests

pH (2.4.24). 4.5 to 5.5.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture A. 2 volumes of *trifluoroacetic acid* and 100 volumes of *water*.

Solvent mixture B. 10 volumes of solvent mixture A, 25 volumes of *acetonitrile*, 30 volumes of *propan-2-ol* and 35 volumes of *stabiliser-free tetrahydrofuran*.

Test solution. Disperse a quantity of the gel containing 1 mg of Adapalene in 7 ml of *stabiliser-free tetrahydrofuran* and mix with the aid of ultrasound. Add 6.0 ml of *propan-2-ol*, shake, add 2 ml of solvent mixture A and dilute to 20.0 ml with *acetonitrile*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with solvent mixture B.

Reference solution (b). A solution containing 0.0025 per cent w/v, each of *adapalene impurity A IPRS* and *adapalene impurity D IPRS* in a mixture of equal volume of *stabiliser-free tetrahydrofuran* and *water*. Dilute 1.0 ml of the solution to 100.0 ml with the same solvent.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 20.0 ml with solvent mixture B.

Chromatographic system

- a stainless steel column 25 cm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as LiChrospher RP 18),
- mobile phase: A. a mixture of 0.2 volume of *trifluoroacetic acid* and 100 volumes of *water*,
  B. a mixture of 40 volumes of *stabiliser-free tetrahydrofuran* and 60 volumes of *water*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer- fluorimetric detector with:
  Excitation wavelength set at 260nm,
  Emission wavelength set at 380 nm for 0−11 minutes and 347 nm for 11−30 minutes,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	40	60

3	17	83
30	17	83
31	40	60
40	40	60

Name	Relative retention time
Adapalene impurity A[1]	0.5
Adapalene (retention time: about 6.5 minutes)	1.0
Adapalene impurity D[2]	3.1

[1]2,2′-binaphthalene-6,6′-dicarboxylic acid,
[2]1,1′-[4,4′-bis(methoxy)biphenyl-3,3′-diyl]bis(tricyclo[3.3.1.1^{3,7}]decane).

Inject reference solution (b) to identify the peaks due to adapalene impurity A and adapalene impurity D.

Inject reference solution (a), (b), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity A or impurity D is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 percent).

The sum of all the specified and unspecified impurities is not more than 1.0 per cent.

Other tests. Comply with the tests stated under Gels.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 21 volumes of *water*, 36 volumes of *stabiliser-free tetrahydrofuran* and 43 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the gel containing 1 mg of Adapalene in 10 ml of *stabiliser-free tetrahydrofuran* and shake with the aid of ultrasound for 5 minutes and dilute to 50.0 with the solvent mixture and filter (0.2 µm Dynagard PP filter).

Reference solution. A 0.01 per cent w/v solution of *adapalene IPRS* in *stabiliser-free tetrahydrofuran*. Dilute 1.0 ml of the solution to 5.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel pre-column 4 mm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- a stainless steel column 25 cm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as LiChrospher 100 RP 18),
- mobile phase: a mixture of 43 volumes of *acetonitrile*, 36 volumes of *stabiliser-free tetrahydrofuran*, 21 volumes of *water*, and 0.02 volume of *trifluoroacetic acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 25 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 4500 theoretical plates.

Inject the reference solution and the test solution.

Calculate the content of $C_{28}H_{28}O_3$ in the gel.

Storage. Store at a temperature not exceeding 30º.