Thalidomide

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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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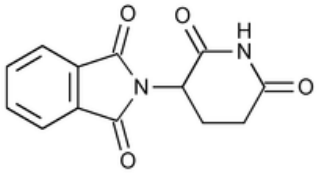
Thalidomide



$C_{13}H_{10}N_2O_4$ Mol. Wt. 258.2

Thalidomide is 1*H*-Isoindole-1,3(2*H*)-dione, 2-(2,6-dioxo-3-piperidinyl)-, (±).

Thalidomide contains not less than 98.0 per cent and not more than 101.5 per cent of $C_{13}H_{10}N_2O_4$, calculated on the anhydrous basis.

Category. Anticancer.

Description. A white to off-white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *thalidomide IPRS* or with the reference spectrum of thalidomide.

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

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture (a). 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *orthophosphoric acid*.

Solvent mixture (b). A 1 per cent v/v solution of *orthophosphoric acid* in *water*.

Solvent mixture (c). 80 volumes of *acetonitrile* and 5 volumes of *water.*

Test solution. Dissolve 0.1 g of the substance under examination in solvent mixture (a) with the aid of ultrasound and dilute to 50.0 ml with solvent mixture (a). To 5.0 ml of the solution, add 5.0 ml of solvent mixture (b) and dilute 50.0 ml with water.

Reference solution (a). A 0.1 per cent w/v solution of *thalidomide IPRS* in *acetonitrile.*

Reference solution (b). Dissolve 0.1 g of *phthalic acid* in 85 ml of solvent mixture (c) and dilute to 100.0 ml with *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with *acetonitrile.*

Reference solution (c). Dilute 1.0 ml, each of, reference solution (a) and (b) to 50.0 ml with solvent mixture (a).

Reference solution (d). Transfer 10.0 ml of reference solution (c) to a 100-ml volumetric flask, add 10 ml of solvent mixture (b) and dilute to volume with *water.*

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous or nonporous silica (4 µm) (Such as Nova-Pak C18),
- mobile phase: A: a mixture of 5 volumes of *acetonitrile*, 95 volumes of *water* and 0.1 volume of *orthophosphoric acid*,

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B: a mixture of 15 volumes of *acetonitrile*, 85 volumes of *water* and 0.1 volume of *orthophosphoric acid*,

- flow rate:2 ml per minute,
- spectrophotometer set at 218 nm,
- injection volume: 200 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
15	50	50
20	100	0
30	100	0

NOTE—The relative retention times with reference to thalidomide, for phthalic acid is about 0.35.

Inject reference solution (d). The test is not valid unless the tailing factor is not more than 2.0, for both the peaks and the relative standard deviation for replicate injections is not more than 2.0 per cent, for phthalic acid peak.

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the phthalic acid peak in the chromatogram obtained with reference solution (d) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 3 times the area of the phthalic acid peak in the chromatogram obtained with reference solution (d) (0.3 per cent).

Limit of Glutamine. Determine by thin-layer chromatography (2.4.17), coating the plate with silica gel G.

Mobile phase. A mixture of 75 volumes of *methylene chloride*, 25 volumes of *methanol* and 0.05 volume of *acetic acid*.

Solvent mixture. Equal volume of *acetonitrile* and *water*.

Test solution. Dissolve 20 mg of the substance under examination in *acetonitrile* and dilute to 10.0 ml with *acetonitrile*.

Reference solution. A 0.01 per cent w/v solution of *glutamine IPRS* in the solvent mixture.

Apply to the plate 2 µl of the reference solution and 100 µl of the test solution. After development, dry the plate in a current of warm air and spray with 0.2 per cent w/v solution of *ninhydrin* in *ethanol*. Heat the plate at 110º for 10 minutes. Any secondary spot corresponding to glutamine in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (0.1 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water (2.3.43). Not more than 0.5 per cent, using *anhydrous dimethyl sulphoxide* as solvent, Method 3.

Microbial contamination (2.2.9). Total aerobic viable count is not more than 1000 CFU per g and total fungal and yeasts count is not more than 100 CFU per g.

Assay. Determine by liquid chromatography (2.4.14).

Solution A. A 1 per cent v/v solution of *orthophosphoric acid* in *water.*

Internal standard solution. A 0.15 per cent w/v solution of *phenacetin* in *acetonitrile.*

Test solution. Dissolve 0.1 g of the substance under examination in *acetonitrile* and dilute to 100.0 ml with *acetonitrile.* Transfer 10.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml of internal standard solution and 10.0 ml of solution A, dilute to volume with *water.*

Reference solution. A 0.1 per cent w/v solution of *thalidomide IPRS* in *acetonitrile.* Transfer 10.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml of internal standard solution and 10.0 ml of solution A, dilute to volume with *water.*

Chromatographic system

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- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous or nonporous silica (4 µm) (Such as Nova-Pak C18),
- mobile phase: a mixture of 15 volumes of *acetonitrile*, 85 volumes of *water* and 0.1 volume of *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 237 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to thalidomide and phenacetin (internal standard) is not less than 3.0, the tailing factor is not more than 2.0 and the relative standard deviation for peak area ratio due to thalidomide and phenacetin (internal standard) for the replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{10}N_2O_4$, using ratio of peak area of thalidomide to that of peak area of phenacetin (internal standard).

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

2.4.26. Solubility.

Insert before **Theophylline.** Page 295

Thalidomide. Very soluble in *dimethyl sulphoxide*; sparingly soluble in *ethanol* and in *water*.

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