Polyethylene Glycol 3350

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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. 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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Polyethylene Glycol 3350

Macrogol 3350

Polyethylene Glycol 3350 is an addition polymer of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups. The apparent weight-average molecular weight is 3015–3685 g per mol (Da). It contains not less than 97.0 per cent and not more than 103.0 per cent of polyethylene glycol 3350, calculated on the anhydrous basis. It may contain a suitable antioxidant.

Category. Pharmaceutical aid (suppository base).

Description. A white, hard, wax-like solid, powder or flakes.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *polyethylene glycol 3350 IPRS* or with the reference spectrum of polyethylene glycol 3350.

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 7.5, determined in a solution prepared by dissolving 5.0 g of the substance under examination in 100.0 ml *carbon dioxide-free water* and 0.3 ml *saturated potassium chloride solution*.

NOTE—The test should be carried out maintaining a temperature of 25 ± 2°.

Apparent weight – average molecular weight and polydispersity. Determine by liquid chromatography (2.4.14).

Test solution. A 0.1 per cent w/v of substance under examination in the mobile phase.

Reference solutions. A 0.1 per cent w/v, solution each of *polyethylene glycol 1000 Da IPRS, polyethylene glycol 2000 Da IPRS, polyethylene glycol 3000 Da IPRS, polyethylene glycol 4000 Da IPRS* and *polyethylene glycol 6000 Da IPRS* in the mobile phase separately in five individual flasks.

NOTE – Filter the reference solutions and the test solution using 0.45 µm PTFE filter and discard the initial 2.0 ml of the solution prior to analysis.

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm packed with polymethacrylate gel, having the capacity to separate proteins over a range of 2000 Da to 40,000 Da (6 µm),
- column temperature: 35º
- mobile phase: *water*,
- flow rate: 0.8 ml per minute,
- detector: differential refractive index detector, maintained at 35º ,
- injection volume: 10 µl.

Inject the reference solutions and the test solution, and determine the elution peak maxima and the corresponding retention times for the respective reference solutions.

Plot the retention times on the x-axis against the log M_P (M_P : peak molecular weights) on the y-axis for the peaks from the polyethylene glycol reference solution to generate a calibration curve using a suitable GPC/SEC software.

Using the same GPC/SEC software, determine the number- and weight-average molecular weights, M_N and M_W, in g per mol (Da), respectively, for the chromatogram of the test solution.

Calculate the polydispersity for Polyethylene Glycol 3350 using the following expression:

Polydispersity= M_W/M_N

where,

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M_W = weight-average molecular weight from the test solution (g per mol)

M_N = number-average molecular weight from the test solution (g per mol)

The apparent weight-average molecular weight is not less than 3015 g per mol and not more than 3685 g per mol.

Polydispersity is not less than 90 per cent and not more than 110 per cent of the value stated on label.

Ethylene glycol and diethylene glycol. Not more than 0.062 per cent w/w (620 ppm) of ethylene glycol and not more than 0.2 per cent w/w (2000 ppm) for the sum of ethylene glycol and diethylene glycol. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1g of the of substance under examination in *water.*

Reference solution. A solution containing 0.001 per cent w/v, each of, *ethylene glycol IPRS* and *diethylene glycol IPRS* in *water.*

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm packed with polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contains some residual cationic functional groups, having the capacity to separate compounds with a molecular weight ranging from 100 to 3000 (as determined by polyethylene oxide), applied to neutral and anionic water-soluble polymers; having a porosity of 125 Å,
- column temperature: 35°
- mobile phase: A 0.005 per cent w/v solution of *sodium azide* in *water*
- flow rate: 0.5 ml per minute
- differential refractive index detector maintained at 35°.
- injection volume: 100 µl

The relative retention time with respect to diethylene glycol for ethylene glycol is 1.1.
Inject reference solution.

The test is not valid unless the resolution between the peaks due to diethylene glycol and ethylene glycol is not less than 0.9.

Inject the reference solution and the test solution.

Calculate the percentage of ethylene glycol and diethylene glycol in the portion of polyethylene glycol.

Ethylene Oxide and Dioxan. Not more than 0.0001 per cent w/w (1 ppm) of ethylene oxide and not more than 0.001 per cent w/w (10 ppm) of dioxan respectively. Determine by gas chromatography (2.4.13).

NOTE— 1. Ethylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated fume hood, using great care. Store all solutions in a hermetic container, and refrigerate at a temperature between 4° and 8°.

2. Before using the polyethylene glycol 200 in this test, remove any volatile components from it by placing 500 mL of polyethylene glycol 200 in a 1000 mL round-bottom flask, attaching the flask to a rotary evaporator maintained at a temperature of 60° and under a vacuum of 10–20 mm Hg for 6 hours.

Acetaldehyde solution. A 0.001 per cent w/v solution of *acetaldehyde* in *water. (Note—prepare the solution immediately before use)*

Ethylene Oxide solution. Dilute 0.5 ml of a 5.0 per cent w/v solution of *ethylene oxide* in *methylene chloride* to 50.0 ml with *water.* (*Note—The solution is stable for 3 months if stored in vials with polytetrafluoroethylene (polytef)-coated silicon membrane crimped caps at −20°. Allow the solution to come to room temperature before use*). Dilute 1.0 ml of the solution to 250.0 ml with *water* to obtain a solution having a concentration of 0.0002 per cent w/v of *ethylene oxide.*

DRAFT FOR COMMENTS

NOTE—Use the solution immediately after preparation.

Dioxan solution. A 0.0005 per cent w/v solution of *dioxan* in *water.* Dilute 1.0 ml of the solution to 100.0 ml with *water.*

Test solution. Transfer 1.0 g of the substance under examination into a 10-mL headspace vial. Add 2.0 ml of *water*, seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully.

Reference solution (a). Transfer 12.0 ml of ethylene oxide solution and 5.0 ml of dioxane solution into a 50 ml volumetric flask and dilute to volume with *water*.

Reference solution (b). Transfer 1.0 g of substance under examination to a 10 ml headspace vial. Add 2.0 mL of reference solution (a), seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully.

Reference solution (c). Transfer 2.0 ml each of acetaldehyde solution and ethylene oxide solution to a 10.0 ml headspace vial, seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully

Chromatographic system

- a fused silica capillary column 50 m x 0.53 mm packed with 5 per cent phenyl and 95 per cent methyl polysiloxane (film thickness 5.0 µm).
- Temperature:
  Column. 70° to 250° @10° per minute, and hold at 250° for 5 minutes.
  Inlet port at 85° and detector port at 250°
- flow rate. 4 ml per minute using helium as carrier gas.
- Injection volume: 1 ml
- Split ratio: 3.5:1

Headspace conditions:

- Vial equilibration temperature: 80°
- Vial equilibration time: 30 minutes

The relative retention time with reference to ethylene oxide for dioxan is about 1.9.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to acetaldehyde and ethylene oxide is not less than 2.0.

Inject reference solution (b) and the test solution.
Calculate the content of ethylene oxide and dioxan (in ppm).

Formaldehyde and acetaldehyde. Determine by liquid chromatography (2.4.14). Not more than 30 ppm of formaldehyde and not more than 200 ppm of the sum of formaldehyde and acetaldehyde.

NOTE—Use amber coloured containers and autosampler vials

2,4-dinitrophenylhydrazine solution: Dissolve 0.25 g of *2,4-dinitrophenylhydrazine* (2,4-DNPH) in 20.0 ml of *acetonitrile* and 3.0 ml of *hydrochloric acid*. Sonicate if required and dilute to 50.0 ml with *acetonitrile*.

Formaldehyde-2,4-DNPH solution: A 0.01 per cent w/v equivalent of aldehyde in *acetonitrile.*

Acetaldehyde-2,4-DNPH solution: A 0.1 per cent w/v equivalent of aldehyde in *acetonitrile*.

Formaldehyde stock solution: Transfer 500 µl of formaldehyde-2,4-DNPH solution to a 10-ml volumetric flask and dilute to volume *acetonitrile. [The formaldehyde concentration is 5 µg per ml]*

DRAFT FOR COMMENTS

Acetaldehyde stock solution: Transfer 500 µl of acetaldehyde-2,4-DNPH solution to a 10-mk volumetric flask and dilute to volume with *acetonitrile*. *[The acetaldehyde concentration is 50 µg per ml]*

Test solution: Dissolve 0.5 g of substance under examination in 1.0 ml of *acetonitrile* and add 2.0 ml of 2,4-DNPH solution. Wait for 15 minutes to allow the solutions to react and dilute to 10.0 ml with *acetonitrile*.

Reference solution: Dilute 1.5 ml of formaldehyde stock solution and 1.2 ml of acetaldehyde stock solution to 10.0 ml of *acetonitrile*.

Chromatographic system

- a stainless steel column 15 cm x 3.0 mm packed with octylsilane bonded to porous silica (3.5 µm), (Pore size: 80 Å)
- column temperature: 30º,
- mobile phase: A: *water*,
  B: *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.65 ml per minute,
- spectrophotometer set at 360 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile Phase B (per cent v/v)
0	50	50
11	0	100
12	50	50
20	50	50

The relative retention times with reference to formaldehyde for acetaldehyde is 1.2.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to formaldehyde and acetaldehyde is not less than 2.0.

Inject the reference solution and the test solution.

Calculate the contents of formaldehyde and acetaldehyde.

Hydroxyl value (2.3.27). 30 to 38.

NOTE—Use amber coloured bottles.

Phthalic anhydride solution. Dissolve 49.0 g of *phthalic anhydride* in 300 ml of *pyridine*, taken from a freshly opened bottle or *pyridine* that has been freshly distilled over *phthalic anhydride*. Shake vigorously until completely dissolved. Add 7 g of *imidazole*, swirl carefully to dissolve, and allow to stand for 16 hours before using.

Test solution. Carefully introduce 25.0 ml of phthalic anhydride solution into a dry, heat-resistant pressure bottle, add 12.0 g of the substance under examination. Add 25 ml of *pyridine*, from a freshly opened bottle or *pyridine* that has been freshly distilled over *phthalic anhydride*. Swirl to dissolve, insert the stopper in the bottle, and wrap it securely in a cloth bag.

Blank. 25.0 ml of phthalic anhydride solution and any additional *pyridine* added to the bottle.

Immerse the bottle in a water bath maintained at a temperature between 96° and 100°, to the same depth as that of the mixture in the bottle. Remove the bottles from the bath after 5 minutes and, without unwrapping, swirl for 30 seconds to homogenize. Heat in the water bath for 60 minutes, then remove from the bath, and allow it to cool to room temperature. Uncap the bottle carefully to release any pressure, remove from the bag, add 10 ml of *water*, and swirl thoroughly. Wait for 2 minutes, add 0.5 ml of 1 per cent w/v solution of *phenolphthalein* in *pyridine* and titrate with *0.5 M sodium hydroxide* to the first pink colour that persists for 15 seconds. Carry out a blank titration.

Calculate the hydroxyl value using the following expression:

$$\text{Result} = [M_r \times (V_B - V_S) \times N]/W$$

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M_r = molecular weight of potassium hydroxide, 56.11

V_B = volume of 0.5 M sodium hydroxide consumed in the blank (ml)

V_S = volume of 0.5 M sodium hydroxide consumed in the test solution (ml)

M = exact molarity of the sodium hydroxide solution

W = weight of substance under examination (g)

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 2.0 g.

Water (2.3.43). Not more than 1.0 per cent, determined on 2.0 g.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.2g of the substance under examination in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution. A 2.0 per cent w/v solution of *polyethylene glycol 3350 IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm and a guard column 4 cm x 6 mm, both, packed with polymethacrylate resin cross-linked with polyhydroxylated ether, having the capacity to separate compounds with a molecular weight range from 100 Da to 5000 Da and having some residual carboxyl functionality (6 µm)
- column temperature: 35º,
- mobile phase: a 0.005 per cent w/v solution of *sodium azide* in *water*,
- flow rate: 0.8 ml per minute,
- detector: differential refractive index maintained at 35º,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 1.5 per cent.

Inject the reference solution and the test solution.

Calculate the percentage of polyethylene glycol 3350, $H[OCH_2CH_2]_nOH$

Storage. Store protected from light and moisture at a temperature not exceeding 30°. Avoid exposure to excessive heat.

Labelling: Label states, 1. Its polydispersity (M_W/M_N) or its polydispersity range.

2. The name and amount of any added antioxidant.

Solubility: Freely soluble in *water*; soluble in *acetone*, in *ethanol (95 per cent)*, in *chloroform*, in *ethylene glycol monoethyl ether*, in *ethyl acetate*, and in *toluene*; insoluble in *ether* and in *hexane.*

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