Polyethylene Glycol

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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

Macrogol

Polyethylene Glycol is a mixture of the polycondensation products of ethylene oxide and water obtained under the controlled conditions. It is represented by the formula $H(OCH_2CH_2)_n OH$, where *n* represents the average number of oxyethylene groups. The average molecular weight is not less than 95.0 per cent and not more than 105.0 per cent of the stated nominal value, if the stated nominal value is less than 1000:not less than 90.0 per cent and not more than 110.0 per cent of the stated nominal value, if the labeled nominal value is between 1000 and 7000: not less than 87.5 per cent and not more than 112.5 per cent of the labeled nominal value, if the labeled nominal value is more than 7000. It may contain a suitable antioxidant.

Category. Pharmaceutical aid (ointment base).

Description. *Liquid grade*: a clear to slightly hazy, colorless or practically colorless, slightly hygroscopic viscous liquid having a slight characteristic odour.

Solid grade: a white waxy plastic material having a consistency similar to bee wax, practically odourless, tasteless or creamy white flakes, beads or powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *polyethylene glycol 200 IPRS* (for polyethylene glycol 200) or *polyethylene glycol 400* (for polyethylene glycol 300 to 600) or *polyethylene glycol 4000 IPRS* (for polyethylene glycol 1000 to 8000) or with reference spectra of polyethylene glycol 200, polyethylene glycol 400 and polyethylene glycol 4000 respectively.

For polyethylene glycol 200. Locate peak maxima of the following major peaks at about 832 cm^{-1}, 885 cm^{-1}, 941 cm^{-1}, 1066 cm^{-1}, 1110 cm^{-1}, 1249 cm^{-1}, 1294 cm^{-1}, 1350 cm^{-1}, 1458 cm^{-1} and 2870 cm^{-1}.

For polyethylene glycol 300 to 600. Locate peak maxima of the following major peaks at about 844 cm^{-1}, 885 cm^{-1}, 941 cm^{-1}, 1110 cm^{-1}, 1249 cm^{-1}, 1294 cm^{-1}, 1350 cm^{-1}, 1458 cm^{-1} and 2869 cm^{-1}.

For polyethylene glycol 1000 to 8000. Locate peak maxima of the following major peaks at about 842 cm^{-1}, 947 cm^{-1}, 1061 cm^{-1}, 1110 cm^{-1}, 1147 cm^{-1} , 1241 cm^{-1}, 1280 cm^{-1}, 1342 cm^{-1}, 1360 cm^{-1} , 1467 cm^{-1} and 2880 cm^{-1}.

Note—

1. *The peak maxima in the spectrum obtained with the substance under examination differs by not more than ±10 cm^{-1} from the spectrum obtained with reference substance.*
2. *Due to peak width, peak maxima for peaks at 832 cm^{-1}, 941 cm^{-1},1110 cm^{-1} and 2870 cm^{-1} (for polyethylene glycol 200), 941 cm^{-1} and 1110 cm^{-1}(for polyethylene glycol 300 to 600) and 947 cm^{-1} and 1110 cm^{-1}(for polyethylene glycol 1000 to 8000), may have a larger shift compared to the listed peak position.*

B. **Ethylene glycol and diethylene glycol**. *(For polyethylene glycol having a nominal molecular weight of 200 to 1000).* Not more than 0.062 per cent w/w (620 ppm) of ethylene glycol and not more than 0.25 per cent w/w (2500 ppm) of the sum of ethylene glycol and diethylene glycol (for polyethylene glycol having molecular weight of 200 to 400) and not more than 0.062 per cent w/w (620 ppm) of ethylene glycol and not more than 0.10 per cent w/w (1000 ppm) of diethylene glycol *(*for polyethylene glycol having molecular weight of more than 400 to 1000*)*.

Determine by gas chromatography (2.4.13).

Test solution. Dissolve 2 g of the substance under examination and 2 mg of *butane-1,3-diol IPRS* in *acetone* and dilute to 50.0 ml with *acetone*.

Reference solution. A solution containing 0.0025 per cent w/v of *ethylene glycol IPRS* and 0.004 per cent w/v each of *diethylene glycol IPRS* and *butane-1,3-diol IPRS* (internal standard) in *acetone*.

Chromatographic system

- a fused silica capillary column 30 m x 0.53 mm packed with 50 per cent phenyl and 50 per cent methyl polysiloxane (film thickness 1.0µm) (such as Rtx-50)
- temperature:

- column: initial temperature 40°, 40° to 60° @ 10° per minute, hold at 60° for 5 minutes, 60° to 170° @ 10° per minute and from 170° to 280° @ 15° per minute and hold at 280° for 0 minutes for the reference solution and 60 minutes for the test solution and acetone (blank),
- inlet port at 270° and detector at 290°,
- flame ionization detector,
- flow rate: 5.0 ml per minute, using helium as carrier gas,
- injection volume: 1µl,
- split ratio: 2:1 (*NOTE— Use general purpose taper, deactivated glass wool liner),*
- run time: 26 minutes for the reference solution and 86 minutes for the test solution and acetone (blank).

The relative retention times with reference to butane-1,3-diol for ethylene glycol and diethylene glycol are 0.45, and 1.25 respectively.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to ethylene glycol and butane-1,3-diol is not less than 20 and between the peaks due to butane-1,3-diol and diethylene glycol is not less than 20, the tailing factor of each peak is not less than 0.8 and not more than 1.8 and the relative standard deviation of the ratio of the peak area of the respective glycol (ethylene glycol and diethylene glycol) to that of the peak area of butane-1,3-diol (internal standard), for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution.

Calculate the percentage of ethylene glycol and diethylene glycol in the portion of polyethylene glycol using ratio of the peak area of the respective glycol (ethylene glycol and diethylene glycol) to that of peak area of butane-1,3-diol (internal standard).

Tests

Appearance of solution (2.4.1). A 10.0 per cent w/v solution is clear and colourless for liquid grades and is slightly hazy and colourless for solid grades.

pH (2.4.24). 4.5 to 7.5, determined in a solution prepared by dissolving 5.0 g in 100.0 ml *carbon-dioxide free water* and 0.3 ml *saturated potassium chloride solution*.

Viscosity (2.4.28). Determine the viscosity by using a Capillary viscometer giving a flow time of not less than 200s and using a liquid bath maintained between 98.6° to 99.2°. The viscosity is within limits specified in Table-1. For a polyethylene glycol not listed in the table, calculate the limits by interpolation.

Table-1

Nominal Average Molecular Weight	Viscosity Range (Centistokes)	Nominal Average Molecular Weight	Viscosity Range (Centistokes)
200	3.9–4.8	2400	49–65
300	5.4–6.4	2500	51–70
400	6.8–8.0	2600	54–74
500	8.3–9.6	2700	57–78
600	9.9–11.3	2800	60–83
700	11.5–13.0	2900	64–88
800	12.5–14.5	3000	67–93
900	15.0–17.0	3250	73–105
1000	16.0–19.0	—	—
1100	18.0–22.0	3500	87–123
1200	20.0–24.5	3750	99–140
1300	22.0–27.5	4000	110–158
1400	24–30	4250	123–177
1450	25–32	4500	140–200
1500	26–33	4750	155–228

1600	28–36	5000	170–250
1700	31–39	5500	206–315
1800	33–42	6000	250–390
1900	35–45	6500	295–480
2000	38–49	7000	350–590
2100	40–53	7500	405–735
2200	43 – 56	8000	470–900
2300	46 – 60	--	---

Limit of free ethylene oxide and 1,4-dioxane. Determine by Head space (with balanced pressure automatic head space sampler) gas chromatography (2.4.13).

*Stripped polyethylene glycol 400***:** Into a 5000-ml, three-neck round bottom flask equipped with a stirrer, a gas dispersion tube and a vacuum outlet, place 3000 g of *polyethylene glycol 400.* At room temperature, evacuate the flask carefully to a pressure of less than 1 mm of mercury, applying the vacuum slowly while observing for excessive foaming due to entrapped gasses. After any foaming has subsided and while stirring continuously, sparge with nitrogen, allowing the pressure rise to 10 mm of mercury. Continue stripping for a minimum of 1 hour. Completeness of stripping procedure should be verified by making a head space injection of the stripped polyethylene glycol 400 (*NOTE-The 10 mm value is a guideline. Deviations from this value affect only the total time required to strip polyethylene glycol 400).* Shut off the vacuum pump and bring the flask pressure back to atmospheric pressure, while maintaining nitrogen sparging, then turn off the gas flow. Transfer stripped polyethylene glycol 400 to a suitable nitrogen filled container.

Test solution. Weigh and transfer 1 g of the substance under examination to a 22-ml pressure headspace vial, seal with a silicone septum with or without pressure relief star spring and a pressure relief safety aluminum sealing cap, and crimp the cap closed with a cap-sealing tool.

Reference solution (a). Weigh and transfer 4.9 g of stripped polyethylene glycol 400 to a 22-ml pressure headspace vial, add 48 µl of *1,4-dioxane* equivalent to 50 mg of *1,4-dioxane* from a syringe, seal and cap the vial. Using the special handling described in the following, complete the preparation.

CAUTION-Ethylene dioxide and 1,4-dioxane are toxic and flammable. Prepare these solutions in a well-ventilated fume hood.

NOTE—Ethylene oxide is a gas at room temperature. It is usually stored in a lecture-type gas cylinder or small metal pressure bomb. Chill the cylinder in a refrigerator before use.

Transfer 5 ml of the liquid *ethylene oxide* to a 100-ml beaker chilled in wet ice, using a gas- tight syringe that has been chilled in a refrigerator, transfer 57 µl of the liquid *ethylene oxide* to the mixture contained in the head space vial and mix. With the aid of a syringe, transfer 2 ml of the solution to a 5-ml beaker. Transfer 1.0 ml of the solution to a 100-ml volumetric flask and dilute to volume with stripped polyethylene glycol 400. Dilute 10.0 ml of the solution to 100.0 ml with the stripped polyethylene glycol 400 and mix. The resulting solution is having known concentration of 10 ppm for both ethylene oxide and 1,4-dioxane. Transfer 1.0 ml of the solution to a 22 ml pressure head space vial, seal with a silicone septum with or without a pressure relief star spring and a pressure safety aluminum sealing cap and crimp, the cap closed with a cap sealing tool.

Reference solution (b). Transfer 4.9 g of stripped polyethylene glycol 400 to 22-ml pressure head space vial, add 50 µl of *acetaldehyde* into the vial. Using the special handling as described under reference solution (a), transfer 50.0 µl of liquid *ethylene oxide* into the vial. Immediately seal the vial and shake. Transfer 1.0 ml of this solution to a 100-ml volumetric flask and dilute to volume with the stripped polyethylene glycol 400. Transfer 1.0 ml of the solution to a 22-ml pressure head space vial, seal with silicone septum with or without a pressure relief star spring and a pressure relief safety aluminum sealing cap and crimp the cap closed with a cap sealing tool.

Chromatographic system

- a fused-silica capillary column 50 m x 0.32 mm, packed with 5 per cent phenyl and 95 per cent methyl polysiloxane (film thickness 5 µm),
- temperature:
  column initially at 70º and then from 70° to 250° @ 10° per minute,
- inlet port at 85º and detector at 250º,
- flame ionization detector,

- flow rate: 2.9 ml per minute, using helium as carrier gas,
- injection volume: 1 ml of head space using a 2-ml gas syringe preheated in an oven at 90°.

The relative retention times with reference to ethylene oxide for acetaldehyde and 1,4-dioxane are about 0.9 and 3.4, respectively.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to acetaldehyde and ethylene oxide is not less than 1.3.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ethylene oxide and 1,4-dioxane, each of, is not more the area of the corresponding peaks in the chromatogram obtained with reference solution (a) (10 ppm).

Ethylene glycol and diethylene glycol. *(For polyethylene glycol having a nominal molecular weight more than 1000 to 8000).* Not more than 0.062 per cent w/w (620 ppm) of ethylene glycol and not more than 0.10 per cent w/w (1000 ppm) of diethylene glycol. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1 g of the substance under examination in *water* and dilute to 100.0 ml with *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
- run time: 30 minutes

The relative retention times of diethylene glycol and ethylene glycol are 1.0 and 1.1 respectively.

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.

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 25.0 g using a platinum dish.

Assay.

Average molecular weight.

Phthalic anhydride solution. Dissolve 49 g of *phthalic anhydride* in 300 ml of *pyridine* from a freshly opened bottle or *pyridine* that has been 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.

NOTE—Use amber coloured bottle to prepare and store this solution.

Test solution. (for liquid polyethylene glycols). Carefully introduce 25.0 ml of phthalic anhydride solution into a dry heat-resistant pressure bottle. Add an amount of the substance under examination equivalent to its expected average molecular weight divided by 160. Insert the stopper in the bottle and wrap it in a securely cloth bag.

Test solution. (for solid polyethylene glycols). Prepare test solution as specified under liquid polyethylene glycols, however amount of the substance under examination should not more than 25 g, because of limited solubility.

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

Immerse the bottles in a water bath maintained at a temperature between 96° and 100° to the same depth as that of mixture in the bottle. Remove the bottles from water bath after 5 minutes without unwrapping, swirl for 30 seconds to homogenize. Heat in the water bath for 30 minutes (60 minutes for polyethylene glycol having molecular weights of 3000 or more) then remove from the water bath and allow to cool to room temperature.

Uncap the bottles carefully to release the pressure, remove from the bag, add 10 ml of *water* and swirl thoroughly. Wait for 2 minutes, add 0.5 ml of a 1 per cent v/v solution of *phenolphthalein* in *pyridine*. Titrate with *0.5 M sodium hydroxide* to the first pink colour that persist for 15 seconds. Carry out a blank titration.

Calculate the average molecular weight using following expression;

$$\text{Average molecular weight} = \frac{2000 \text{ x } W}{(Vb - Vs) \text{ x } M}$$

Where, *W* = weight of the substance under examination taken for the test solution.

Vb = volume of *0.5 M sodium hydroxide* consumed by the blank (ml).

Vs = volume of *0.5 M sodium hydroxide* consumed by the substance under examination (ml)

M = molarity of the *sodium hydroxide solution*.

Storage. Store protected from moisture.

Labelling. Label states, as part of the official title, the average nominal molecular weight of polyethylene glycol and name and quantity of any added antioxidant.

Solubility: Liquid grades are soluble with *water*; solid grades are freely soluble in *water*; and all are soluble in *acetone*, in *alcohol*, in *chloroform*, in *ethylene glycol monoethyl ether*, in *ethyl acetate*, and in *toluene*; all are insoluble in *ether* and in *hexane.*