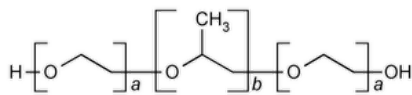


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Poloxamer



$\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$   
Oxirane, methyl-, polymer with oxirane;  
 $\alpha$ -Hydro- $\omega$ -hydroxypoly(oxyethylene)<sub>a</sub>-poly(oxypropylene)<sub>b</sub>-poly(oxyethylene)<sub>a</sub> block copolymer, in which *a* and *b* have the values shown in the following table:

Poloxamer	<i>a</i>	<i>b</i>
124	12	20
188	80	27
237	64	37
338	141	44
407	101	56

Polyethylene-polypropylene glycol  
CAS RN®: 9003-11-6.

Change to read:

DEFINITION

Poloxamer is a synthetic block copolymer of ethylene oxide and propylene oxide. It is available in several types, conforming to the requirements shown in the following table.

Poloxamer	Physical Form	Average Molecular Weight	Weight (% Oxyethylene)	Unsaturation (mEq/g)
124	Liquid	2090–2360	46.7 ± 1.9	▲NMT 0.028▲ (NF 1-Dec-2021)
188	Solid	7680–9510	81.8 ± 1.9	▲NMT 0.034▲ (NF 1-Dec-2021)
237	Solid	6840–8830	72.4 ± 1.9	▲NMT 0.042▲ (NF 1-Dec-2021)
338	Solid	12,700–17,400	83.1 ± 1.7	▲NMT 0.039▲ (NF 1-Dec-2021)

Poloxamer	Physical Form	Average Molecular Weight	Weight (% Oxyethylene)	Unsaturation (mEq/g)
407	Solid	9840–14,600	73.2 ± 1.7	▲NMT 0.065▲ (NF 1-Dec-2021)

It may contain a suitable antioxidant.

## IDENTIFICATION

### • A. [SPECTROSCOPIC IDENTIFICATION TESTS \(197\)](#), [Infrared Spectroscopy](#): 197F

Use a thin film of melted specimen if it is a solid. Use [USP Poloxamer Liquid RS](#) for Poloxamer 124, and use [USP Poloxamer Solid RS](#) for Poloxamer 188, 237, 338, and 407. Because of the differences in the ratios of copolymer composition, the intensity of some absorption bands may vary.

## ASSAY

### • AVERAGE MOLECULAR WEIGHT

**Phthalic anhydride–pyridine solution:** Dissolve 144 g of phthalic anhydride in freshly opened or freshly distilled pyridine containing less than 0.1% of water, and dilute with pyridine to 1000 mL. Protect from light, and allow to stand overnight. To verify that the *Phthalic anhydride–pyridine solution* has adequate strength, pipet 10 mL into a 250-mL conical flask, add 25 mL of pyridine and 50 mL of water, and after 15 min add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), then titrate with 0.5 N sodium hydroxide VS: it consumes between 37.6 and 40.0 mL of 0.5 N sodium hydroxide.

**Analysis:** Weigh a suitable quantity, not exceeding 15 g, of Poloxamer, calculated by multiplying the average molecular weight by 0.004, into a glass-stoppered, 250-mL boiling flask. Carefully pipet 25 mL of *Phthalic anhydride–pyridine solution* into the flask, touching the tip of the drained pipet to the protrusion in the flask. Add a few glass beads, and swirl to dissolve the specimen. Pipet 25 mL of *Phthalic anhydride–pyridine solution* into a second, glass-stoppered, conical flask, add a few glass beads, and use as the reagent blank. (An additional 25-mL portion of pyridine may be added to both the test specimen and reagent blank, before refluxing, if necessary to ensure fluidity.) Heat both flasks, fitted with suitable reflux condensers, and allow to reflux for 1 h. Allow to cool, and pour two 10-mL portions of pyridine through each condenser. Remove the flasks from the condensers, add 10 mL of water to each, insert the stoppers, swirl, and allow to stand for 10 min. To each flask add 50.0 mL of 0.66 N sodium hydroxide and 0.5 mL of a solution (1 in 100) of phenolphthalein in pyridine. Titrate with 0.5 N sodium hydroxide VS to a light pink endpoint that persists for NLT 15 s.

Calculate the average molecular weight:

$$\text{Result} = 2000 \times W / [(V_B - V_S) \times N]$$

$W$  = weight of the sample taken (g)

$V_B$  = volume of 0.5 N sodium hydroxide VS consumed by the blank (mL)

$V_S$  = volume of 0.5 N sodium hydroxide VS consumed by the residual acid in the test solution (mL)

$N$  = actual normality of 0.5 N sodium hydroxide VS

**Acceptance criteria:** See the table in the *Definition*.

### • WEIGHT PERCENT OXYETHYLENE

**Solvent:** Use deuterated water or deuteriochloroform.

**NMR reference:** Use sodium 2,2-dimethyl-2-silapentane-5-sulfonate (for deuterated water) or tetramethylsilane (for deuteriochloroform).

**Sample solution:** Dissolve 0.1–0.2 g of Poloxamer in deuterated water containing 1% of sodium 2,2-dimethyl-2-silapentane-5-sulfonate to obtain 1 mL of solution, or, if the Poloxamer does not dissolve in water, use deuteriochloroform containing 1% of tetramethylsilane as the solvent.

### Instrumental conditions

(See [Nuclear Magnetic Resonance Spectroscopy \(761\)](#), [Qualitative and Quantitative NMR Analysis, Quantitative Applications, 1. Relative quantitation](#).)

**Mode:** Nuclear magnetic spectrometry

**Sample size:** 0.5–1.0 mL of the *Sample solution*

### Analysis:

**Sample:** *Sample solution*

Transfer the *Sample solution* to a standard 5-mm NMR spinning tube, and if deuteriochloroform is the solvent, add 1 drop of deuterated water, and shake the tube. Scan the region at 0–5 ppm, and use the calculation formulas specified below. Record as  $A_1$  the average area of the doublet appearing at about 1.08 ppm, representing the methyl groups of the oxypropylene units, and record as  $A_2$  the average area of the composite band at a range of 3.2–3.8 ppm, due to the  $\text{CH}_2\text{O}$  groups of both the oxyethylene and oxypropylene units and also the CHO groups of the oxypropylene units, with reference to the sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane singlet at 0 ppm.

Calculate the percentage of oxyethylene, by weight, in the Poloxamer taken:

$$\alpha = (A_2/A_1) - 1$$

$A_2$  = average area of the composite band at a range of 3.2–3.8 ppm

$A_1$  = average area of the doublet appearing at about 1.08 ppm

$$\text{Result} = 3300 \times \alpha / (33 \times \alpha + 58)$$

**Acceptance criteria:** See the table in the *Definition*.

#### • UNSATURATION

**Solution A:** Place 50 g of mercuric acetate in a 1000-mL volumetric flask, and dissolve with 900 mL of methanol to which 0.5 mL of glacial acetic acid has been added. Dilute with methanol to volume, and mix. Discard the solution if it is yellow. If it is turbid, filter it. Discard it if it is still turbid. Use fresh reagents if it is necessary to repeat the preparation of the solution. Protect the solution from light by storing it in an amber bottle in the dark.

**Sample:** 15.0 g

**Analysis:** Transfer the *Sample* to a 250-mL conical flask. Pipet 50 mL of *Solution A* into the flask, and mix on a magnetic stirrer until solution is complete. Allow to stand for 30 min with occasional swirling. Add 10 g of sodium bromide crystals, and stir on a magnetic stirrer for 2 min. Without delay, add 1 mL of phenolphthalein TS, and titrate the liberated acetic acid with 0.1 N methanolic potassium hydroxide VS. Perform a blank determination. Determine also the initial acidity as follows. Dissolve 15.0 g of Poloxamer in 75 mL of methanol that has been neutralized with methanolic potassium hydroxide to the phenolphthalein endpoint. Add 1 mL of phenolphthalein TS, and titrate with the same 0.1 N methanolic potassium hydroxide VS under a nitrogen sweep.

Calculate the unsaturation, in mEq/g:

$$\text{Result} = (V_U - V_B - V_A) \times N/15$$

$V_U$  = volume of 0.1 N methanolic potassium hydroxide used for titrating the test specimen (mL)

$V_B$  = volume of 0.1 N methanolic potassium hydroxide used for titrating the blank (mL)

$V_A$  = volume of 0.1 N methanolic potassium hydroxide used for titrating the initial acidity (mL)

$N$  = normality of the titrant

**Acceptance criteria:** See the table in the *Definition*.

#### IMPURITIES

**Change to read:**

##### • LIMIT OF FREE ETHYLENE OXIDE, PROPYLENE OXIDE, AND 1,4-DIOXANE

**Stripped poloxamer:** Place 500 g of Poloxamer 124 into a suitable 3-neck, round-bottom flask equipped with a stirrer, a thermometer, a vacuum outlet, and a heating mantle. Evacuate the flask carefully at room temperature to a pressure of less than 10 mm of mercury, applying the vacuum slowly to avoid excessive foaming due to entrapped gases. After any foaming has subsided, heat the flask to 80° and continue to apply vacuum for 2 h and then cool to room temperature. Shut off the vacuum pump, and introduce nitrogen to bring the flask pressure back to atmospheric pressure. Transfer the *Stripped poloxamer* to a suitable nitrogen-filled container.

##### Standard solution

[CAUTION—Ethylene oxide, propylene oxide, and 1,4-dioxane are toxic and flammable. Prepare these solutions in a well-ventilated fume hood.] To a tared vial that can be sealed, add 50.0 g of *Stripped poloxamer*. Add 60  $\mu\text{L}$  of 1,4-dioxane and 75  $\mu\text{L}$  of propylene oxide from a chilled syringe. Add ethylene oxide, using the following special handling procedure. Ethylene oxide, which is a gas at room temperature, is usually stored in a lecture-type gas cylinder or a 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 15  $\mu\text{L}$  of the liquid ethylene oxide to the mixture. Immediately seal the vial, and shake on a vortex mixer for at least 30 s. Transfer 0.20 g

of this solution to a tared vial that can be sealed, and add *Stripped poloxamer* to obtain a *Standard solution* having a final weight of 50.0 g. Each gram of this *Standard solution* contains 1 µg of ethylene oxide, 5 µg of propylene oxide, and 5 µg of 1,4-dioxane. Transfer  $1.00 \pm 0.01$  g of this solution to a 22-mL pressure headspace vial, and add about 0.01 g of butylated hydroxytoluene. Seal with a silicone septum with or without a pressure-relief star spring and with a pressure-relief, aluminum, safety sealing-cap, and crimp the cap closed with a cap-sealing tool.

**Sample solution:** Transfer  $1.00 \pm 0.01$  g of Poloxamer to a 22-mL pressure headspace vial, and add 0.01 g of butylated hydroxytoluene. Seal, cap, and crimp as directed for the *Standard solution*.

#### Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

**Mode:** GC (equipped with a balanced-pressure automated headspace sampler)

**Detector:** Flame ionization

**Column:** 0.32-mm × 50-m fused-silica capillary; 5-µm layer of stationary phase [G27](#) coating

#### Temperatures

**Detector:** 250°

**Injector:** 250°

**Transfer line:** 140°

**Column:** See [Table 1](#).

**Table 1**

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	—	70	10
70	10	240	10

**Carrier gas:** Helium

**Flow rate:** 1.6 mL/min

**Injection size:** Separately place the vials containing the *Standard solution* and the *Sample solution* in the automated sampler, and start the sequence so that the vial is heated at a temperature of 110° for 30 min before a suitable portion of its headspace is injected into the chromatograph.

#### Autosampler

**Needle-withdrawal time:** 0.3 min

**Pressurization time:** 1 min

**Injection time:** 0.08 min

**Vial pressure:** 22 ▲psi ▲ (NF 1-Dec-2021) with the vial vent off

#### System suitability

**Sample:** *Standard solution*

[NOTE—The relative retention times for ethylene oxide, propylene oxide, and 1,4-dioxane are about 1.0, 1.3, and 3.8, respectively.]

#### Suitability requirements

**Resolution:** NLT 2.0 between ethylene oxide and propylene oxide

**Relative standard deviation:** NMT 15%

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the concentrations, in µg/g, of ethylene oxide, propylene oxide, and 1,4-dioxane in the portion of Poloxamer taken:

$$\text{Result} = (r_U/r_S) \times C$$

$r_U$  = peak response from the *Sample solution*

$r_S$  = peak response from the *Standard solution*

$C$  = concentration of ethylene oxide, propylene oxide, or 1,4-dioxane in the *Standard solution* (µg/g)

#### Acceptance criteria

Ethylene oxide: NMT 1 µg/g  
Propylene oxide: NMT 5 µg/g  
1,4-Dioxane: NMT 5 µg/g

SPECIFIC TESTS

- **pH** (791): 5.0–7.5, in a solution (1 in 40)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. No storage requirements are specified.
- **LABELING:** Label it to state, as part of the official title, the Poloxamer number. Label it to indicate the name and quantity of any antioxidant.
- **USP REFERENCE STANDARDS** (11).  
[USP Poloxamer Liquid RS](#)  
[USP Poloxamer Solid RS](#)

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
POLOXAMER	<a href="#">Documentary Standards Support</a>	CE2020 Complex Excipients
REFERENCE STANDARD SUPPORT	RS Technical Services <a href="mailto:RSTECH@usp.org">RSTECH@usp.org</a>	CE2020 Complex Excipients

Chromatographic Database Information: [Chromatographic Database](#)

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