pump *Mobile phase* through the column at this flow rate for at least 1 h before the first injection. Check the flow gravimetrically, and adjust it if necessary. Reduce the flow rate to about 0.1 mL/min when the system is not in use.]

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Chromatograph five replicate injections of the *Standard solution*, allowing 15 min between injections, and record the retention times of the components of the *Standard solution.*

Insert the average retention time along with the molecular weight of each component in the *Standard solution* into the calibration table of the molecular weight distribution software. Check the regression results for a cubic fit of the calibration points, and obtain a correlation coefficient, R, for the line.

Suitability requirements

Retention time: The retention times for each component determined on replicate injections agree within ±2 s.

Resolution: Dextrose and stachyose are baseline resolved from one another and from the 5800-MW pullulan standard.

[NOTE—Prominent negative baseline valleys are usually observed between the peaks for the 5800-, 23,700-, and 100,000-MW pullulan standards.]

Correlation coefficient R: NLT 0.9999

Analysis

Samples: *Standard solution* and *Sample solution*

Use the molecular weight distribution software of the data reduction system to generate a molecular weight distribution plot of Hydrogenated Polydextrose.

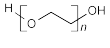
Acceptance criteria: No measurable peak above a molecular weight of 22,000 is found.

- **pH** ⟨**791**⟩**:** 5.0–7.0, in a solution (1 in 10)
- **Water Determination,** *Method I* ⟨**921**⟩**:** NMT 4.0%. Use a mixture of Hydranal Solvent and Hydranal Formamide dry (2:1) as a solvent. Perform the titration at 50° in a jacketed beaker.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store in a cool and dry place.
- **USP Reference Standards** ⟨**11**⟩
  USP 1,6-Anhydro-D-glucose RS
  USP Dextrose RS
  USP Polydextrose RS
  USP Sorbitol RS

Polyethylene Glycol



Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-; Polyethylene glycol [25322-68-3].

DEFINITION

Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented:

$$H(OCH_2CH_2)_nOH$$

in which *n* represents the average number of oxyethylene groups. The average molecular weight is NLT 95.0% and NMT 105.0% of the labeled nominal value if the labeled nominal value is less than 1000; it is NLT 90.0% and NMT 110.0% of the labeled nominal value if the labeled nominal value is between 1000 and 7000; and it is NLT 87.5% and NMT 112.5% of the labeled nominal value if the labeled nominal value is more than 7000. It may contain a suitable antioxidant.

ASSAY

- **Average Molecular Weight**

Phthalic anhydride solution: Place 49.0 g of phthalic anhydride into an amber bottle, and dissolve in 300 mL of pyridine 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 h before using.

Sample solution for liquid Polyethylene Glycols: Carefully introduce 25.0 mL of the *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an amount of the specimen equivalent to its expected average molecular weight divided by 160. Insert the stopper in the bottle, and wrap it securely in a cloth bag.

Sample solution for solid Polyethylene Glycols: Carefully introduce 25.0 mL of *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an amount of the specimen equivalent to its expected molecular weight divided by 160; however, because of limited solubility, do not use more than 25 g. 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* plus any additional pyridine added to the bottle

Analysis: 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 min and, without unwrapping, swirl for 30 s to homogenize. Heat in the water bath for 30 min (60 min for Polyethylene Glycols having molecular weights of 3000 or more), 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 2 min, add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), and titrate with 0.5 N sodium hydroxide VS to the first pink color that persists for 15 s. Perform a blank determination.

Calculate the average molecular weight taken:

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

W = weight of the Polyethylene Glycol taken for the *Sample solution* (g)

V_B = volume of 0.5 N sodium hydroxide consumed by the *Blank* (mL)

V_S = volume of 0.5 N sodium hydroxide consumed by the specimen (mL)

N = normality of the sodium hydroxide solution

Acceptance criteria: See *Table 1*.

Table 1

Label Claim (Nominal Value)	Acceptance Criteria
<1000	95.0–105.0%
1000–7000	90.0–110.0%
>7000	87.5–112.5%

IMPURITIES

- **Residue on Ignition** ⟨**281**⟩

Sample: 25 g

Analysis: Proceed as directed, using a platinum dish and moistening the residue with 2 mL of sulfuric acid.

Accceptance criteria: NMT 0.1%

- **Heavy Metals** ⟨**231**⟩

Test preparation: 4.0 g in 5.0 mL of 0.1 N hydrochloric acid. Dilute with water to 25 mL.

Acceptance criteria: NMT 5 ppm

- **LIMIT OF FREE ETHYLENE OXIDE AND 1,4-DIOXANE**

Stripped polyethylene glycol 400: Into a 5000-mL, 3-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 gases. After any foaming has subsided and while stirring continuously, sparge with nitrogen, allowing the pressure to rise to 10 mm of mercury. Continue stripping for a minimum of 1 h. Completeness of the stripping procedure should be verified by making a headspace 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 the Polyethylene Glycol 400.]

Shut off the vacuum pump, and bring the flask pressure back to atmospheric pressure while maintaining nitrogen sparging. Remove the gas dispersion tube with the gas still flowing, and then turn off the gas flow. Transfer the *Stripped polyethylene glycol 400* to a suitable nitrogen-filled container.

Standard solution: Transfer 4.90 g of *Stripped polyethylene glycol 400* to a tared 22-mL pressure headspace vial that can be sealed. Add 48 µL of 1,4-dioxane, equivalent to 50 mg of 1,4-dioxane, from a syringe; seal; and cap the vial. [**CAUTION—**Ethylene oxide and 1,4-dioxane are toxic and flammable. Prepare these solutions in a well-ventilated fume hood.]

Using the special handling described in the following, complete the preparation. 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, equivalent to 50 mg of ethylene oxide, to the mixture contained in the headspace vial, and mix. With the aid of a syringe, transfer 2 mL of this solution to a 5-mL beaker. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Stripped polyethylene glycol 400* to volume. Transfer 10 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix to obtain a *Standard solution* having known concentrations of 10 µg/g for both ethylene oxide and 1,4-dioxane. Transfer 1.0 mL of the *Standard solution* to a 22-mL pressure headspace vial, seal with a 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.

System suitability solution: Transfer 4.90 g of *Stripped polyethylene glycol 400* to a 22-mL pressure headspace vial. Pipet 50 µL of acetaldehyde into the vial. Using the special handling described in *Standard solution,* 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 with *Stripped polyethylene glycol 400* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Stripped polyethylene glycol 400* to volume. Transfer 1.0 mL of this *System suitability solution* to a 22-mL pressure headspace vial, and seal, cap, and crimp as directed for the *Standard solution.*

Sample solution: Transfer 1.0 g of Polyethylene Glycol to a 22-mL pressure headspace vial, and seal, cap, and crimp as directed for the *Standard solution.*

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability.*)
Mode: Headspace GC (balanced pressure automatic headspace sampler)
Detector: Flame ionization
Column: 0.32-mm × 50-m fused-silica capillary column containing bonded phase G27 in a 5-µm film thickness
Temperature
Column: See *Table 2.*

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	10	250	—

Injector: 85°
Detector: 250°
Flow rate: 2.9 mL/min
Carrier gas: Helium
Injection size: 1.0 mL of headspace using a 2-mL gas syringe preheated in an oven at 90°

System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for acetaldehyde and ethylene oxide are about 0.9 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.3 between the acetaldehyde peak and the ethylene oxide peak

Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—The relative retention times for ethylene oxide and 1,4-dioxane are about 1.0 and 3.4, respectively.]
Place the vials containing the *Standard solution* and the *Sample solution* into the automated sampler, and heat the vials at a temperature of 80° for 30 min.
[NOTE—A headspace apparatus that automatically transfers the measured amount of headspace may be used to perform the injection.]

Acceptance criteria: The peak areas for ethylene oxide and 1,4-dioxane of the *Sample solution* are not greater than those of the corresponding peaks of the *Standard solution* corresponding to NMT 10 µg/g of ethylene oxide and NMT 10 µg/g of 1,4-dioxane.

- **LIMIT OF ETHYLENE GLYCOL AND DIETHYLENE GLYCOL** (for Polyethylene Glycol having a nominal molecular weight less than 450)

Standard solution: 0.5 mg/mL each of ethylene glycol and of diethylene glycol in water
Sample solution: 400 mg/mL of Polyethylene Glycol in water
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability.*)
Mode: GC
Detector: Flame ionization
Column: 3-mm × 1.5-m stainless steel; packing of 12% G13 on support S1NS
Temperature
Column: 140°
Injector port: 250°
Detector: 280°
Carrier gas: Nitrogen or another suitable inert gas
Flow rate: 50 mL/min
Injection size: 2.0 µL

Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—The elution order is ethylene glycol followed by diethylene glycol.]
Calculate the percentage of ethylene glycol in the portion of Polyethylene Glycol taken:

$$\text{Result} = (r_{U1}/r_{S1}) \times (C_{S1}/C_U) \times 100$$

r_{U1} = peak height of ethylene glycol from the *Sample solution*
r_{S1} = peak height of ethylene glycol from the *Standard solution*
C_{S1} = concentration of ethylene glycol in the *Standard solution* (mg/mL)

C_U = concentration of Polyethylene Glycol in the *Sample solution* (mg/mL)

Calculate the percentage of diethylene glycol in the portion of Polyethylene Glycol taken:

$$\text{Result} = (r_{U2}/r_{S2}) \times (C_{S2}/C_U) \times 100$$

r_{U2} = peak height of diethylene glycol from the *Sample solution*

r_{S2} = peak height of diethylene glycol from the *Standard solution*

C_{S2} = concentration of diethylene glycol in the *Standard solution* (mg/mL)

C_U = concentration of Polyethylene Glycol in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.25% of the sum of ethylene glycol and diethylene glycol is found.

- **LIMIT OF ETHYLENE GLYCOL AND DIETHYLENE GLYCOL** (for Polyethylene Glycol having a nominal molecular weight 450 or more but NMT 1000)

Ceric ammonium nitrate solution: 6.25 g of ceric ammonium nitrate in 100 mL of 0.25 N nitric acid. Use within 3 days.

Standard stock solution: 2.5 mg/mL of diethylene glycol in 1:1 freshly distilled acetonitrile:water

Sample stock solution: Dissolve 50.0 g of Polyethylene Glycol in 75 mL of diphenyl ether, previously warmed if necessary, just to melt the crystals, in a 250-mL distilling flask. Slowly distill at a pressure of 1–2 mm of mercury, into a receiver graduated to 100 mL in 1-mL subdivisions, until 25 mL of distillate has been collected. Add 20.0 mL of water to the distillate, shake vigorously, and allow the layers to separate. Cool in an ice bath to solidify the diphenyl ether and facilitate its removal. Filter the separated aqueous layer, wash the diphenyl ether with 5.0 mL of ice-cold water, pass the washings through the filter, and collect the filtrate and washings in a 25-mL volumetric flask. Warm to room temperature, and dilute with water to volume, if necessary. Mix this solution with 25.0 mL of freshly distilled acetonitrile in a glass-stoppered, 125-mL conical flask.

Standard solution: Add 10.0 mL of the *Standard stock solution* to 15.0 mL of *Ceric ammonium nitrate solution*. Within 2–5 min, determine the absorbance of the *Standard solution*.

Sample solution: Add 10.0 mL of the *Sample stock solution* to 15.0 mL of *Ceric ammonium nitrate solution*. Within 2–5 min, determine the absorbance of the *Sample solution*.

Blank: Mixture of 15.0 mL of *Ceric ammonium nitrate solution* and 10.0 mL of 1:1 freshly distilled acetonitrile:water

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: UV-Vis

Cell: 1 cm

Analytical wavelength: 450 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: The absorbance of the *Sample solution* does not exceed that of the *Standard solution*, corresponding to NMT 0.25% of combined ethylene glycol and diethylene glycol.

SPECIFIC TESTS

- **pH** ⟨**791**⟩

Sample solution: 5.0 g of Polyethylene Glycol in 100 mL of carbon dioxide-free water. Add 0.30 mL of saturated potassium chloride solution.

Acceptance criteria: 4.5–7.5

- **COMPLETENESS AND COLOR OF SOLUTION:** A solution of 5 g of Polyethylene Glycol in 50 mL of water is colorless; it is clear for liquid grades and NMT slightly hazy for solid grades.
- **VISCOSITY** ⟨**911**⟩**:** Determine its viscosity by using a capillary viscosimeter giving a flow time of NLT 200 s and using a liquid bath maintained at 98.9 ± 0.3° (210° F). The viscosity is within the limits specified in *Table 3*. For a Polyethylene Glycol not listed in the table, calculate the limits by interpolation.

Table 3

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	3350	76 –110
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	—	—

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol. Label it to indicate the name and quantity of any added antioxidant.

Polyethylene Glycol Ointment

» Prepare Polyethylene Glycol Ointment as follows:

Polyethylene Glycol 3350	400 g
Polyethylene Glycol 400	600 g
to make	1000 g

Heat the two ingredients on a water bath to 65°. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of the polyethylene glycol 400 with an equal amount of polyethylene glycol 3350.

NOTE—If 6 percent to 25 percent of an aqueous solution is to be incorporated in Polyethylene Glycol Ointment, replace 50 g of the polyethylene glycol 3350 with an equal amount of stearyl alcohol.