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Polyoxyl 15 Hydroxystearate

12-Hydroxyoctadecanoic acid polymer with α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl);
Polyethylene glycol 15 hydroxystearate
CAS RN®: 70142-34-6.

DEFINITION

Polyoxyl 15 Hydroxystearate results from the reaction of about 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid. The product consists mainly of 12-hydroxystearic acid polyethoxylated at both the carboxyl and the hydroxyl groups with polyethylene glycol. It contains free polyethylene glycols.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197F** .▲ (CN 1-May-2020) If the sample is solid or too viscous for thin film formation, the sample should be gently warmed to achieve a mobile liquid, which may then be used to prepare the thin film.

• **B.** **Thin-Layer Chromatographic Identification Test ⟨201⟩**

Sample solution: To 1.0 g of Polyoxyl 15 Hydroxystearate add 100 mL of a 100-mg/mL solution of potassium hydroxide, and boil under a reflux condenser for 30 min. Acidify the warm solution with 20 mL of hydrochloric acid, and cool to room temperature. Shake the mixture with 50 mL of ether, and allow to stand until a separation of the layers is visible. Separate the clear upper layer, add 5 g of anhydrous sodium sulfate, wait for 30 min, filter, and evaporate to dryness on a water bath. Dissolve 50 mg of the residue in 25 mL of ether.

Standard solution: 2 mg/mL of USP 12-Hydroxystearic Acid RS in methylene chloride

Plate: Octadecylsilyl silica gel for chromatography as the coating substance

Application volume: 2 µL

Developing solvent system: Acetone, methylene chloride, and glacial acetic acid (50:10:40)

Spray reagent: Prepare a solution of 80 mg/mL of phosphomolybdic acid in 2-propanol.

Analysis: Proceed as directed in the chapter. Develop over two-thirds of the plate, and dry in a current of cold air. Then spray the plate with *Spray reagent*, heat the plate at 120° for 1–2 min, and locate the spots on the plate.

Acceptance criteria: The R_F value and color of the principal spot of the *Sample solution* correspond to those of the *Standard solution*.

• **C.** It meets the requirements of the test for *Free Polyethylene Glycols*.

COMPOSITION

• **Free Polyethylene Glycols**

Mobile phase: Methanol and water (8:2)

Standard solution A: 1.6 mg/mL of USP Polyethylene Glycol 1000 RS in *Mobile phase*

Standard solution B: 0.8 mg/mL of USP Polyethylene Glycol 1000 RS in *Mobile phase*, diluted from *Standard solution A* in *Mobile phase*

Sample solution: 4.8 mg/mL of Polyoxyl 15 Hydroxy stearate in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: Refractive index

Columns: 7.8-mm × 30-cm analytical column; 6-µm packing L39 and a 12-nm pore size; two 4-mm × 12.5-cm precolumns; 5-µm packing L1 and a 10-nm pore size.

Connect both precolumns to the analytical column using a 3-way valve, and switch the *Mobile phase* flow according to the following program. [Note—Shown in *Figure 1*, the analysis is started with precolumn 2 and an analytical column in series. After about 114 s, the valves, controlled by the detector program, switch over such that the eluent flows past precolumn 2, and direct to precolumn 1 and the

analytical column. The columns are switched when the components to be determined, but not the interfering matrix, are ready to reach the analytical column. Simultaneously, precolumn 2 is washed out in the reverse direction by a second pump to remove the unwanted matrix components.]

Time (s)	Program
0–114	Precolumn 2 and analytical column
115–end	Precolumn 1 and analytical column
115–420	Reverse flow of precolumn 2

Temperature

Column: Room temperature

Detector: Room temperature

Flow rate: 1.1 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution A*

Suitability requirements

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Calculate the percentage of polyethylene glycols in the portion of Polyoxyl 15 Hydroxystearate taken:

$$\text{Result} = 2 \times (C_S/C_U)[r_U/(r_{S1} + 2r_{S2})] \times 100$$

C_S = concentration of USP Polyethylene Glycol 1000 RS in *Standard solution A* (mg/mL)

C_U = concentration of Polyoxyl 15 Hydroxystearate in the *Sample solution* (mg/mL)

r_U = peak response of polyethylene glycol from the *Sample solution*

r_{S1} = peak response of polyethylene glycol 1000 from *Standard solution A*

r_{S2} = peak response of polyethylene glycol 1000 from *Standard solution B*

Acceptance criteria: 27.0%–39.0% of free polyethylene glycols

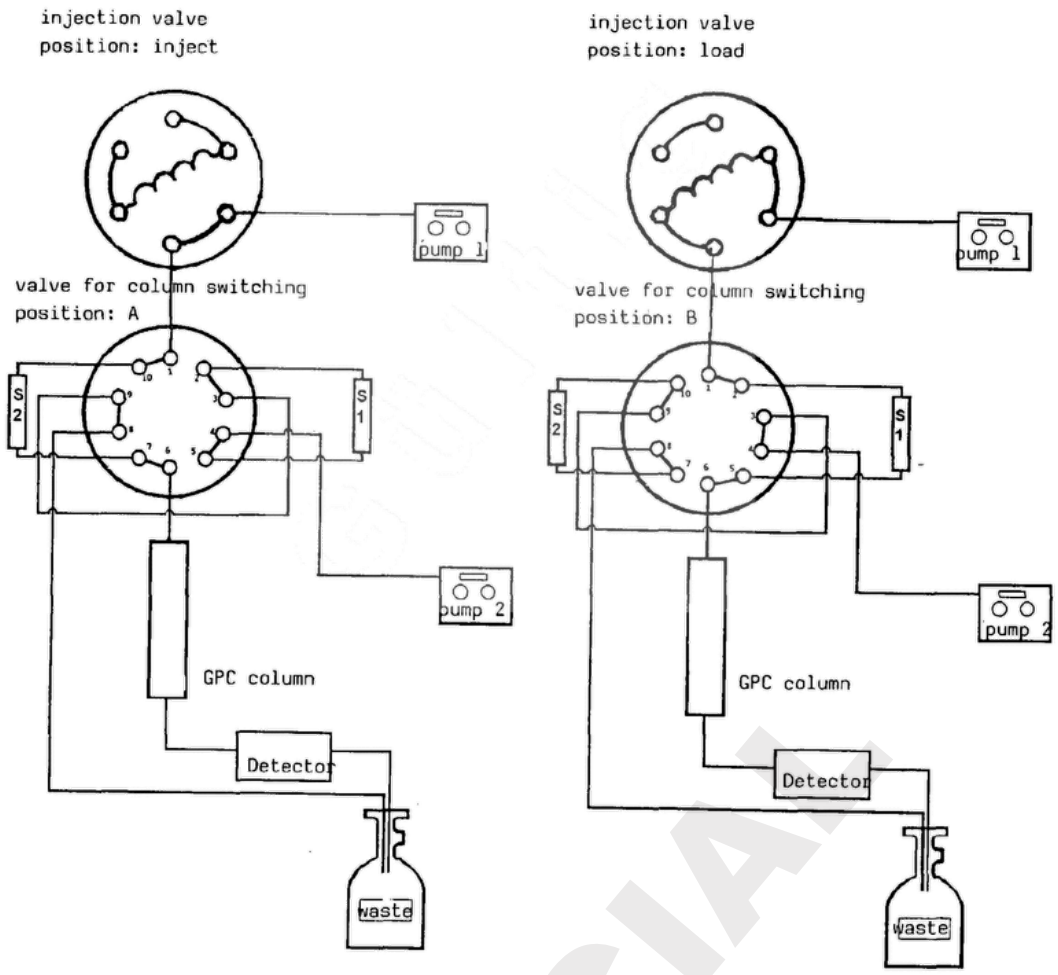

Figure 1. Apparatus

IMPURITIES

Inorganic Impurities

- **Articles of Botanical Origin, *Total Ash*(561):** NMT 0.3%, determined on 1.0 g
- **Limit of Nickel**

[**Caution**—When using closed high-pressure digestion vessels and microwave laboratory equipment, the safety precautions and operating instructions given by the manufacturer must be followed.]

[Note—If an alternative apparatus is used, adjustment of the instrument parameters may be necessary.]

Nickel standard stock solution: Dilute nickel standard solution TS two-fold with water. This solution contains the equivalent of 5 µg/mL of nickel.

Standard solutions: Transfer 25, 50, 75, and 100 µL of *Nickel standard stock solution* to four identical 25-mL volumetric flasks. To each flask add 0.5 mL of a 10-mg/mL solution of magnesium nitrate, 0.5 mL of a 100-mg/mL solution of monobasic ammonium phosphate, and 6.0 mL of nickel-free nitric acid, dilute with water to volume, and mix well. [Note—Content of nickel in the nickel-free nitric acid is NMT 0.005 ppm.] The *Standard solutions* contain 0.005, 0.01, 0.015, and 0.02 µg/mL of nickel, respectively.

Sample solution: Transfer about 250 mg of Polyoxyl 15 Hydroxystearate to a suitable high-pressure-resistant digestion vessel (fluoropolymer or quartz glass), and add 6.0 mL of nickel-free nitric acid and 2.0 mL of 30% hydrogen peroxide. Place the closed vessel in a laboratory microwave oven, and digest using an appropriate program, e.g., 1000 W for 40 min. Allow the digestion vessel to cool down before opening. Add 2.0 mL of 30% hydrogen peroxide, and repeat the digestion step. Allow the digestion vessel to cool down before opening. Quantitatively transfer to a 25-mL volumetric flask, add 0.5 mL of a 10-mg/mL solution of magnesium nitrate and 0.5 mL of a 100-mg/mL solution of monobasic ammonium phosphate, dilute with water to volume, and mix well.

Blank solution: Place 6.0 mL of nickel-free nitric acid and 2.0 mL of 30% hydrogen peroxide in a suitable high-pressure-resistant digestion vessel. Proceed as directed under *Sample solution*, beginning with “Place the closed vessel in a laboratory microwave oven, and digest using an appropriate program, e.g., 1000 W for 40 min.”

Zero solution: In a 50-mL volumetric flask, introduce 1.0 mL of a 10-mg/mL solution of magnesium nitrate, 1.0 mL of a 100-mg/mL solution of monobasic ammonium phosphate, and 12.0 mL of nickel-free nitric acid. Dilute with water to volume, and mix well.

Spectrometric conditions

(See *Atomic Absorption Spectroscopy* ⟨852⟩.)

Mode: Graphite furnace atomic absorption spectrophotometer equipped with a background compensation system, a coated tube resistant to pyrolysis, and a nickel hollow-cathode lamp.

Analytical wavelength: Nickel emission line of 232.0 nm

Temperature: Maintain the drying temperature of the furnace at 120° for 35 s after a 5-s ramp; maintain the ashing temperature at 1100° for 10 s after a 30-s ramp; maintain the cooling temperature at 800° for 5 s after a 5-s decrease; and maintain the atomization temperature at 2600° for 7 s. [Note—The temperature program may be modified to obtain optimum furnace temperatures.]

Analysis

Samples: *Standard solutions*, *Sample solution*, and *Blank solution*

Concomitantly determine the absorbances of the *Samples* using the *Spectrometric conditions* described above. Use the *Zero solution* to set the instrument to zero. Plot the absorbances of the *Standard solutions* versus the concentration, in µg/mL, of nickel, and draw the straight line best fitting the plotted points. From the graph so obtained, determine the concentration, C_T, in µg/mL, of nickel in the *Sample solution*, and determine the concentration, C_B, in µg/mL, of nickel in the *Blank solution*. If necessary, dilute with the *Zero solution* to obtain a reading within the calibrated absorbance range.

Calculate the quantity, in µg, of nickel in each g of Polyoxyl 15 Hydroxystearate taken:

$$\text{Result} = V \times (C_T - C_B)/W$$

V = volume of the *Sample solution* and the *Blank solution*, 25 mL

W = weight of Polyoxyl 15 Hydroxystearate taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 1 µg/g of nickel

Organic Impurities

• **Procedure: Limit of Free Ethylene Oxide and Dioxane**

[Caution—Ethylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated fume hood, using great care. Protect both hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in hermetic containers, and refrigerate at a temperature between 4° and 8°.]

[Note—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 h.]

Acetaldehyde solution: 10 µg/mL of acetaldehyde. [Note—Prepare the *Acetaldehyde solution* immediately prior to use.]

Ethylene oxide stock solution: Fill a chilled pressure bottle with liquid ethylene oxide, and store in a freezer when not in use. Use a small piece of polyethylene film to protect the liquid from contact with the rubber gasket. Tare a glass-stoppered conical flask, add about 50 mL of polyethylene glycol 200, and reweigh the flask. Transfer about 5 mL of the liquid ethylene oxide to a 100-mL beaker chilled in a mixture of sodium chloride and ice (1:3). Using a gas-tight syringe that has been previously cooled to −10°, transfer about 300 µL (corresponding to about 250 mg) of liquid ethylene oxide to the polyethylene glycol 200, and swirl gently to mix. Replace the stopper, reweigh the flask, and determine the amount of ethylene oxide absorbed by weight difference. Adjust the weight of the mixture with polyethylene glycol 200 to 100.0 g, replace the stopper, and swirl gently to mix. This stock solution contains about 2.5 mg/g of ethylene oxide. [Note—Prepare this stock solution immediately prior to use, and store in a refrigerator.]

Ethylene oxide solution: Tare a glass-stoppered conical flask, and chill it in a refrigerator. Add about 35 mL of polyethylene glycol 200, and reweigh the flask. Using a gas-tight gas chromatographic syringe that has been chilled in a refrigerator, transfer about 1 g of the chilled *Ethylene oxide stock solution*, weighed, to the tared, conical flask. Adjust the weight of the solution with polyethylene glycol 200 to 50.0 g, replace the stopper, and swirl gently to mix. Transfer about 10 g of this solution, weighed, to a 50-mL volumetric flask. Add 30 mL of water, and mix. Dilute with water to volume, and mix to obtain a solution containing about 10 µg/mL of ethylene oxide. [Note—Prepare this solution immediately prior to use, and use directly after preparation.]

Dioxane solution: 500 µg/mL of dioxane

Standard solution A: Transfer 0.1 mL of *Ethylene oxide solution* to a 10-mL pressure headspace vial. [Note—Other sizes may be used depending on the operating conditions, however, the same size must be used for *Standard solution A, Standard solution B*, and the *Sample solution*.] Add 0.1 mL of *Acetaldehyde solution* and 0.1 mL of *Dioxane solution*, seal the vial, and mix.

Standard solution B: Transfer about 1.0 g of Polyoxyl 15 Hydroxystearate to another 10-mL pressure headspace vial, add 0.1 mL of *Ethylene oxide solution*, 0.1 mL of *Dioxane solution*, and 1.0 mL of *N,N*-dimethylacetamide. Seal the vial, and mix.

Sample solution: Transfer about 1.0 g of Polyoxyl 15 Hydroxystearate to a 10-mL pressure headspace vial, add 1.0 mL of *N,N*-dimethylacetamide and 0.2 mL of water, seal the vial, and mix.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

[NOTE—The use of a headspace apparatus that automatically transfers a measured amount of headspace is allowed.]

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m glass or quartz capillary; 1.0-µm layer of phase G1

Temperature

Injector port: 150°

Detector: 250°

Column: See the temperature program table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	—	50	5
50	5	180	—
180	30	230	—
230	—	230	5

Carrier gas: Helium

Linear velocity: 20 cm/s

Injection size: 1 mL (the gaseous headspace)

Injection type: Split ratio 20:1

[NOTE—If the headspace apparatus is used, then an injection time of 12 s and a transfer line temperature of 150° are recommended.]

Headspace sampler: Each vial is heated at a temperature of 90° for 45 min, before a suitable portion of its headspace is injected.

System suitability

Sample: *Standard solution A*

[NOTE—The relative retention times for acetaldehyde and ethylene oxide are 0.94 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between acetaldehyde and ethylene oxide

Signal-to-noise ratio: NLT 5, determined from the dioxane peak

Relative standard deviation: NMT 15%

Analysis

Samples:

Standard solution B and *Sample solution*

Using a heated, gas-tight, gas chromatographic syringe, separately inject equal volumes of the gaseous headspace of the *Samples* into the chromatograph, record the chromatograms, and measure the areas for the major peaks: the mean areas of the ethylene oxide and dioxane peaks from the *Sample solution* are not greater than half the mean areas of the corresponding peaks from *Standard solution B*.

Calculate the content of ethylene oxide, in ppm, in the portion of Polyoxyl 15 Hydroxystearate taken:

$$\text{Result} = (A_E \times r_U)/[(r_S \times W_U) - (r_U \times W_S)]$$

A_E = quantity of ethylene oxide added to *Standard solution B* (µg)

r_U = ethylene oxide peak response from the *Sample solution*

r_S = ethylene oxide peak response from *Standard solution B*

W_U = weight of test substance taken to prepare the *Sample solution* (g)

W_S = weight of test substance taken to prepare *Standard solution B* (g)

Calculate the content of dioxane, in ppm, in the portion of Polyoxyl 15 Hydroxystearate taken:

$$\text{Result} = (A_D \times r_U)/[(r_S \times W_U) - (r_U \times W_S)]$$

A_D = quantity of dioxane added to *Standard solution B* (µg)

r_U = dioxane peak response from the *Sample solution*

r_S = dioxane peak response from *Standard solution B*

W_U = weight of test substance taken to prepare the *Sample solution* (g)

W_S = weight of test substance taken to prepare *Standard solution B* (g)

Acceptance criteria

Ethylene oxide: NMT 1 ppm

Dioxane: NMT 50 ppm

SPECIFIC TESTS

- **Fats and Fixed Oils,** *Acid Value* ⟨401⟩**:** NMT 1.0, determined on 2.0 g
- **Fats and Fixed Oils,** *Hydroxyl Value*⟨401⟩**:** 90–110
- **Fats and Fixed Oils,** *Iodine Value, Method I*⟨401⟩**:** NMT 2.0
- **Fats and Fixed Oils,** *Peroxide Value*⟨401⟩**:** NMT 5.0
- **Fats and Fixed Oils,** *Saponification Value*⟨401⟩**:** 53–63
- **Water Determination,** *Method Ia*⟨921⟩**:** NMT 1.0%, determined on 2.0 g

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers at a temperature below 25°.
- **USP Reference Standards** ⟨11⟩

  USP 12-Hydroxystearic Acid RS
  USP Polyethylene Glycol 1000 RS
  USP Polyoxyl 15 Hydroxystearate RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
POLYOXYL 15 HYDROXYSTEARATE	Documentary Standards Support	CE2020 Complex Excipients
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	CE2020 Complex Excipients

Chromatographic Database Information: Chromatographic Database

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