

mL conical flask. Bubble ethylene oxide through the chlorobenzene at a moderate rate for about 30 minutes, insert the stopper, and store protected from heat. Pipet 25 mL of 0.5 N alcoholic hydrochloric acid solution, prepared by mixing 45 mL of hydrochloric acid with 1 L of alcohol, into a 500-mL conical flask containing 40 g of magnesium chloride hexahydrate. Shake the mixture to effect saturation. Pipet 10 mL of the ethylene oxide solution into the flask, and add 20 drops of bromocresol green TS. If the solution is not yellow (acid) at this point, add an additional volume, accurately measured, of 0.5 N alcoholic hydrochloric acid to give an excess of about 10 mL. Record the total volume of 0.5 N alcoholic hydrochloric acid added. Insert the stopper in the flask, and allow to stand for 30 minutes. Titrate the excess acid with 0.5 N alcoholic potassium hydroxide VS. Perform a blank titration, using 10.0 mL of chlorobenzene instead of ethylene oxide solution, adding the same total volume of 0.5 N alcoholic hydrochloric acid, and note the difference in volumes required. Each mL of the difference in volumes of 0.5 N alcoholic potassium hydroxide consumed is equivalent to 22.02 mg of ethylene oxide. Calculate the concentration, in mg per mL, of ethylene oxide in the *Standard solution*. Standardize daily.

Standard preparation—Transfer about 5 g of Polyoxyl 20 Cetostearyl Ether to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene, exactly 50 μ L of *Internal standard solution*, and an accurately measured volume of *Standard solution* containing about 0.5 mg of ethylene oxide. Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Test preparation—Transfer about 5 g of Polyoxyl 20 Cetostearyl Ether, accurately weighed, to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene and 50 μ L, accurately measured, of *Internal standard solution*. Add a volume of chlorobenzene equal to the volume of the *Standard solution* added to prepare the *Standard preparation*. Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Chromatographic system—Under typical conditions, the instrument is equipped with a flame-ionization detector, and contains a 3-mm (OD) $\times$ 1.8-m stainless steel column packed with S3. The injection port and detector block temperatures are maintained at about 210° and 230°, respectively, and the column temperature is maintained at about 160°. Helium is used as the carrier gas at a flow rate of 66 mL per minute.

Interference check—Inject a suitable volume of chlorobenzene into the gas chromatograph, and allow the chromatogram to run until the solvent has eluted. Similarly inject and chromatograph the *Internal standard solution*, the *Standard solution*, and a solution prepared according to the directions for the *Test preparation*, but omitting the internal standard. No interfering peaks are observed.

Procedure—Inject about 2 μ L of the *Standard preparation* into a suitable gas chromatograph, and record the chromatogram. Similarly, inject about 2 μ L of the *Test preparation*, and record the chromatogram. Calculate the weight, in g, of ethylene oxide in the *Test preparation* (W_T) by the formula:

$$(W_E W_U R_U) / 1000 (W_U R_S - W_S R_U)$$

in which W_E is the weight, in mg, of ethylene oxide added to the *Standard preparation*; W_U and W_S are the weights, in g, of Polyoxyl 20 Cetostearyl Ether used to prepare the *Test preparation* and the *Standard preparation*, respectively; and R_U and R_S are the area ratios of ethylene oxide to internal standard in the chromatograms for the *Test preparation* and the *Standard preparation*, respectively. Calculate the percentage of ethylene oxide in the portion of Polyoxyl 20 Cetostearyl Ether taken by the formula:

$$100 W_T / W_U$$

in which W_T and W_U are as defined previously. The limit is 0.01%.

Free polyethylene glycols—Transfer about 12 g, accurately weighed, to a 500-mL separator containing 50 mL of ethyl acetate. Add 50 mL of sodium chloride solution (29 in 100), shake vigorously for 2 minutes, and allow to separate for 15 minutes. Drain the lower, aqueous phase into a second 500-mL separator, and extract the upper layer with a second 50-mL portion of sodium chloride solution (29 in 100). To the combined aqueous layers add 50 mL of ethyl acetate, shake vigorously for 2 minutes, and allow to separate as before. Drain the lower, aqueous phase into a third 500-mL separator, and extract with two 50-mL portions of chloroform, by shaking for 2 minutes each time. Evaporate the combined chloroform extracts in a 150-mL beaker on a steam bath, with the aid of a stream of nitrogen, to apparent dryness. Redissolve in about 15 mL of chloroform, and transfer to a filter, collecting the filtrate in a 150-mL beaker. Rinse the funnel with several small portions of chloroform, and evaporate the combined filtrate and rinsings, as described above, until no odor of chloroform or ethyl acetate is perceptible. Cool in a desiccator, and weigh: the limit is 7.5%.

Average polymer length—Place the Polyoxyl 20 Cetostearyl Ether in a 50° water bath overnight, in order to melt it completely. Shake vigorously to eliminate any possibility of molecular weight gradients within it, and transfer 200 μ L to a 5- $\times$ 180-mm high-resolution NMR sample tube. Add 200 μ L of deuterated chloroform by means of a separate microsyringe. Add 5 drops of tetramethylsilane as an internal reference standard. Cap the tube tightly, and shake thoroughly. Place the tube in the NMR spectrometer, and record the NMR spectrum at an appropriate RF power level and a sweep time of 250 seconds per 500 Hz (see *Qualitative scans* under *Nuclear Magnetic Resonance* (761)). Adjust the spectrum amplitude so that the signal at 1.1 ppm is at least 80% of full-scale. Record the integral areas from 0.4 ppm to 2.35 ppm (A_1), and from 2.35 ppm to 4.9 ppm (A_2) at a sweep time of 50 seconds per 500 Hz at an integral power level such that the integral of the ethylene oxide peak at 3.5 ppm is at least 80% of full chart height. Do not change the power level during the sweep. Record the integral of each peak several times, and calculate the average integral area. Calculate the number of oxyethylene units, n , per molecule taken by the formula:

$$n = (32A_2 / A_1 - 3) / 4$$

in which 32 is the total number of protons in the molecule not activated by oxygen, averaged for the cetyl and stearyl radicals, 3 is the number of oxygen-activated protons not included in the oxyethylene unit count, 4 is the number of protons in each oxyethylene unit.

Polyoxyl 35 Castor Oil

» Polyoxyl 35 Castor Oil contains mainly the tricinoleate ester of ethoxylated glycerol, with smaller amounts of polyethylene glycol ricinoleate and the corresponding free glycols. It results from the reaction of glycerol ricinoleate with about 35 moles of ethylene oxide.

Packaging and storage—Preserve in tight containers.

USP Reference standards (11)—

USP Polyoxyl 35 Castor Oil RS

Identification—

A: *Infrared Absorption* (197F).

B: Dissolve about 0.1 g in 10 mL of alcoholic potassium hydroxide TS, boil for about 3 minutes, and evaporate to dryness. Mix the residue with 5 mL of water: it dissolves, yielding a clear solution. Add a few drops of glacial acetic acid: a white precipitate is formed.

C: To a solution (1 in 20) add bromine TS, dropwise: the bromine is decolorized.

Specific gravity (841): between 1.05 and 1.06.

Viscosity (911): between 600 and 850 centipoises at 25°, a capillary viscometer being used.

Acid value (401): not more than 2.0.

Hydroxyl value (401): between 65 and 80.

Iodine value (401): between 25 and 35.

Saponification value (401): between 60 and 75.

Water, Method I (921): not more than 3.0%.

Residue on ignition (281): not more than 0.3%.

Heavy metals, Method II (231): 0.001%.

Polyoxyl 40 Hydrogenated Castor Oil

» Polyoxyl 40 Hydrogenated Castor Oil contains mainly the tri-hydroxystearate ester of ethoxylated glycerol, with smaller amounts of polyethylene glycol tri-hydroxystearate and of the corresponding free glycols. It results from the reaction of glycerol tri-hydroxystearate with about 40 to 45 moles of ethylene oxide.

Packaging and storage—Preserve in tight containers.

Identification—

A: Dissolve about 0.1 g in 1 mL of water, add 9 mL of sodium chloride solution (1 in 20), and heat in a water bath: the solution becomes turbid at a temperature between 70° and 85°.

B: Dissolve about 0.1 g in 10 mL of alcoholic potassium hydroxide TS, boil for about 3 minutes, and evaporate to dryness. Mix the residue with 5 mL of water: it dissolves, yielding a clear solution. Add a few drops of glacial acetic acid: a white precipitate is formed.

Congealing temperature (651): between 16° and 26°.

Acid value (401): not more than 2.0.

Hydroxyl value (401): between 60 and 80.

Iodine value (401): not more than 2.0.

Saponification value (401): between 45 and 69.

Water, Method I (921): not more than 3.0%.

Residue on ignition (281): not more than 0.3%.

Heavy metals, Method II (231): 0.001%.

Polyoxyl 40 Stearate

Poly(oxy-1,2-ethanediyl), α -hydro- ω -hydroxy-, octadecanoate.

Polyethylene glycol monostearate [9004-99-3].

» Polyoxyl 40 Stearate is a mixture of the monoesters and di-esters of Stearic Acid or Purified Stearic Acid with mixed polyoxyethylene diols, the average polymer length being equivalent to about 40 oxyethylene units.

Packaging and storage—Preserve in tight containers.

USP Reference standards (11)—

USP Polyoxyl 40 Stearate RS

Identification, Infrared Absorption (197M), on undried specimen.

Congealing temperature (651): between 37° and 47°.

Acid value (401): not more than 2.

Hydroxyl value (401): between 25 and 40.

Saponification value (401): between 25 and 35.

Water, Method I (921): not more than 3.0%.

Heavy metals, Method II (231): 0.001%.

Free polyethylene glycols—Transfer about 6 g, accurately weighed, to a 500-mL separator containing 50 mL of ethyl acetate. Dissolve completely, then add 50 mL of sodium chloride solution (29 in 100), shake vigorously for 2 minutes, and allow to separate for 15 minutes. If separation is incomplete, carefully insert the separator into the well of a steam bath for short time intervals. Repeat this technique as many times as necessary to ensure the complete separation of the two phases. Cool, and drain the lower, aqueous, phase into a second 500-mL separator, and extract the upper layer with a second 50-mL portion of sodium chloride solution (29 in 100). Repeat the separation as before, including the steam bath technique to enhance complete separation. To the combined aqueous layers add 50 mL of ethyl acetate, shake vigorously for 2 minutes, and allow to separate as before. Drain the lower, aqueous phase into a third 500-mL separator, and extract it with two 50-mL portions of chloroform, by shaking for 2 minutes each time. Repeat the steam bath technique to ensure complete separation. Evaporate the combined chloroform extracts in a 150-mL beaker on a steam bath, with the aid of a stream of nitrogen, to apparent dryness. Redissolve in about 15 mL of chloroform, and transfer to a filter, collecting the filtrate in a 150-mL beaker. Rinse the funnel with several small portions of chloroform, and evaporate the combined filtrate and rinsings, as described above, until no odor of chloroform or ethyl acetate is perceptible. Dry in vacuum at 60° for 1 hour. Cool in a desiccator, and weigh: not less than 17% and not more than 27% of free polyethylene glycols is found.

Polyoxyl Lauryl Ether

$\text{CH}_3(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_n\text{OH}$, $n = 3-23$

Polyethylene glycol monolauryl ether [9002-92-0].

DEFINITION

Polyoxyl Lauryl Ether is a mixture of the monolauryl ethers of mixed polyethylene glycols, the average polymer length being equivalent to NLT 3 and NMT 23 oxyethylene units (nominal value). It contains various amounts of free lauryl alcohol, and it may contain some free polyethylene glycols.

IDENTIFICATION

• A. INFRARED ABSORPTION (197F)

Sample: Use a thin film of melted Polyoxyl Lauryl Ether if the material is a solid.

Acceptance criteria: Meets the requirements

• B. PROCEDURE

Sample: 0.1 g

Analysis: Dissolve or disperse the *Sample* in 5 mL of alcohol, and add 10 mL of diluted hydrochloric acid, 5 mL of barium chloride TS, and 10 mL of phosphomolybdic acid solution (1 in 10).

Acceptance criteria: A precipitate is formed.

• C. It meets the requirements of the test for *Fats and Fixed Oil, Hydroxyl Values* (401).

IMPURITIES

Organic Impurities

• PROCEDURE: LIMIT OF FREE ETHYLENE OXIDE AND DIOXANE

Analysis: Proceed as directed in *Ethylene Oxide and Dioxane, Method I* (228).