POLYVINYL ALCOHOL (PVA)-POLYETHYLENE GLYCOL (PEG) GRAFT CO-POLYMER

New specifications prepared at the 80th JECFA, and published in FAO JECFA Monographs 17 (2015). The 80th JECFA (2015) considered the additive to be of no safety concern for use in food supplements for the functional uses listed.

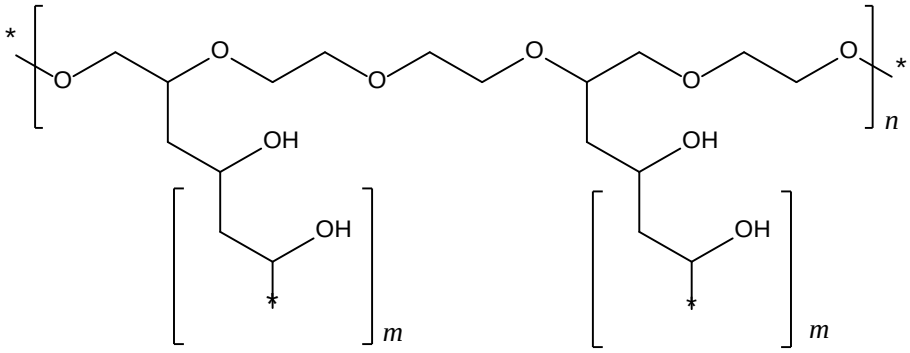
SYNONYMS Macrogol poly(vinyl alcohol) grafted co-polymer; Ethylene glycol and vinyl alcohol graft copolymer; INS No. 1209

DEFINITION Polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft co-polymer is a graft copolymer of ethylene glycol and vinyl alcohol consisting of approximately 75% vinyl alcohol units and 25% ethylene glycol units. The copolymer is produced by grafting polyvinyl acetate onto a backbone of polyethylene glycol followed by hydrolysis of the polyvinyl acetate side chains to form polyvinyl alcohol grafted side chains. The copolymer may contain colloidal silica at levels of 0.3 to 0.5% to improve flow properties.

Chemical names Polyvinyl alcohol-polyethylene glycol-graft-co-polymer; Poly(ethylene glycol)-graft-poly(vinyl alcohol)

C.A.S number 96734-39-3, 121786-16-1

Structural formula



Molecular weight 40,000 to 50,000 Daltons (weight-average)

DESCRIPTION White to pale yellow powder

FUNCTIONAL USES Glazing agent, binder for tablets, stabilizer

CHARACTERISTICS

IDENTIFICATION

Solubility (Vol. 4) Freely soluble in water, dilute acids, and dilute solutions of alkali hydroxides; practically insoluble in ethanol, acetic acid, and acetone.

pH (Vol. 4) 5.0 to 8.0 (20% soln)

Infrared spectrum (Vol. 4) Dissolve 0.2 g in 20 ml of water, spread a few drops of the solution on a thallium bromoiodide plate and evaporate the solvent at 110° for 30 min. The infrared absorption spectrum of the sample corresponds to that of the reference spectrum in Appendix.

Film formation	Dissolve 0.4 g in 2 ml of water. Place 1 ml of the solution on a glass plate and allow to dry. A transparent film is formed.
Viscosity – Rotational method	Less than 250 mPa·s Determine using a 20% solution (m/m), use a viscometer at 25° with a Brookfield RV2 spindle, and a rotation speed of 100 rpm.

PURITY

Loss on drying (Vol. 4)	Not more than 5%. (1.0 g sample, vacuum (<20 mmHg) at 140°, 1 h)
Sulfated ash (Vol. 4)	Not more than 2% (5 g, 650°)
Ester value	Not less than 10 and not more than 75 mg KOH/g See description under TESTS
Vinyl acetate	Not more than 20 mg/kg See description under TESTS
Acetate	Not more than 1.5% See description under TESTS
1,4-Dioxane	Not more than 10 mg/kg See description under TESTS
Ethylene oxide	Not more than 0.2 mg/kg See description under TESTS
Ethylene glycol and diethylene glycol	Not more than 400 mg/kg (singly or in combination) See description under TESTS
Lead (Vol. 4)	Not more than 1 mg/kg Determine using an AAS (Electrothermal atomization technique) appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the methods described in Volume 4 (under “General Methods, Metallic Impurities”).

TESTS

PURITY TESTS

Ester value	Determine the acid value (I_A) as follows. Dissolve 5.00 g of sample in 100 ml of distilled water while stirring with a magnetic stirrer. Titrate with 0.01 M alcoholic potassium hydroxide, determining the end-point potentiometrically. Carry out a blank determination under the same conditions.

$$I_A = \frac{0.561(n_1 - n_2)}{m}$$

Where

n_1 is the volume of titrant used in the test, ml
n_2 is the volume of titrant used in the blank, ml
m is the mass of the sample, g

Determine the saponification value (I_S) as follows. Place 5.00 g of sample in a 250 ml borosilicate glass flask fitted with a reflux condenser. Add 50.0 ml of 0.5 M alcoholic potassium hydroxide and stir vigorously with a magnetic stirrer. Attach the condenser and heat under reflux for 30 min. Add 1 ml of phenolphthalein solution (0.1% (w/w) Phenolphthalein in ethanol) and titrate the excess potassium hydroxide immediately (while still hot) with 0.5 M hydrochloric acid. Carry out a blank determination under the same conditions.

$$I_S = \frac{28.05(n_1 - n_2)}{m}$$

Where

n_1 is the volume of titrant used in the test, ml
n_2 is the volume of titrant used in the blank, ml
m is the mass of the sample, g

The ester value (I_E) is calculated from the saponification value (I_S) and the acid value (I_A):

$$I_E = I_S - I_A$$

Vinyl Acetate

Principle

Determine by liquid chromatography using 1-vinylpyrrolidine-2-one as an internal standard.

Equipment

High performance liquid chromatograph equipped with gradient valve and UV detector
Column: Size: 4.6 mm x 25 cm
Stationary phase: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups (5 µm)
Column temperature: 30 °
A precolumn containing octadecylsilyl silica gel for chromatography (5 µm) may be used if a matrix effect is observed.

Reagents

Vinyl acetate (99.9% purity, Fluka Part No. 46060, or equiv.)
1-vinylpyrrolidin-2-one (>99%, Sigma-Aldrich Part No. V3409, or equiv.)
Acetonitrile, methanol and deionized water (HPLC grade)

Procedure

Preparation of internal standard solution:

Accurately weigh about 5 mg of 1-vinylpyrrolidin-2-one, add 10 ml of methanol and dilute to 50 ml with water in a volumetric flask.

Preparation of standard solution

Accurately weigh about 5.0 mg of vinyl acetate, quantitatively transfer into a 50 ml volumetric flask using 5 ml methanol, add 10 ml of internal standard solution and dilute to volume with water.

Preparation of sample solution

Accurately weigh about 250 mg of sample, transfer to a 10-ml volumetric flask with about 2 ml of methanol, and ultrasonicate, if necessary. After cooling to ambient temperature, dilute with water to volume, and mix. Pass through a 0.2-micron filter.

Mobile phase
Mobile phase A: acetonitrile, methanol, water (5:5:90 V/V/V);
Mobile phase B: methanol, acetonitrile, water (5:45:50 V/V/V);

Time (min)	Solution A (% v/v)	Solution B (% v/v)
0-2	100	0
2-40	100 → 85	0 → 15
40-42	85 → 0	15 → 100

Flow rate: 1.0 ml/min
Detection: 205 nm
Injection: 10 µl
Retention time: Vinyl acetate = about 19 min; 1-vinylpyrrolidin-2-one = about 25 min.

System suitability
Resolution of about 5.0 between the peaks of vinyl acetate and 1-vinylpyrrolidin-2-one shall be obtained.

Analysis
Analyze standard solution and calculate the peak ratio between vinyl acetate and 1-vinylpyrrolidin-2-one peaks. Analyze the sample solution and calculate the peak area ratio between vinyl acetate and 1-vinylpyrrolidin-2-one peaks in the sample solution.

Obtain the concentration of vinyl acetate in the sample from the peak area ratios of sample & internal standard, standard & internal standard, concentration of standard, and weight of sample.

Acetate

Principle
Determine by liquid chromatography using citric acid (internal standard).

Equipment
High performance liquid chromatograph equipped with gradient valve and UV detector;
Column: Size: 4.6 mm x 25 cm
Stationary phase: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups (5 µm)
Column temperature: ambient
A precolumn containing octadecylsilyl silica gel for chromatography (5 µm) may be used if a matrix effect is observed.

Reagents
Acetic acid standard (>99%)
Citric acid standard (>99%)
Deionized water (HPLC grade)

Procedure
Mobile phase
0.50 g/l solution of sulfuric acid

Preparation of internal standard solution
Accurately weigh about 30 mg of citric acid and dilute to 100 ml with mobile phase in a volumetric flask.
Preparation of standard solution

Accurately weigh about 30 mg of acetic acid, add 10 ml of internal standard solution and dilute to 50 ml in a volumetric flask with mobile phase.

Preparation of system suitability solution
Accurately weigh about 30 mg of citric acid, 30 mg of acetic acid, and dilute to 50 ml in a volumetric flask with mobile phase.

Preparation of sample solution
Accurately weigh about 200 mg of sample, add 2 ml internal standard solution and make up to 10 ml in a volumetric flask with mobile phase. Pass through a 0.2-micron filter.

Analysis
Chromatographic conditions
Flow rate: 1 ml/min
Detector: UV 205 nm
Injection: 20 µl
Retention time: acetate = about 5 min; citrate = about 7 min.
After each injection, rinse column with mixtures of equal volumes of acetonitrile and mobile phase.

System suitability
Resolution of about 2.0 between the peaks of acetate and citrate shall be obtained.

Inject standard solution and calculate the peak area ratio between acetate and citrate peaks. Inject sample solution and calculate the peak area ratio between acetate and citrate peaks in the sample solution.

Obtain the concentration of acetate in the sample from the peak area ratios of sample & internal standard, standard & internal standard, concentration of standard, and weight of sample.

Ethylene oxide

Principle
Determine by dynamic headspace (purge & trap) gas chromatography using acetaldehyde as internal standard

Equipment
Gas chromatograph equipped with flame ionization detector and suitable purge & trap system;
Detector temperature: 250°
Column: 0.32-mm × 30-m fused silica capillary column; 1.0-µm layer of dimethylpolysiloxane (e.g., DB-1 from J&W Scientific)

[**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°.]

Reagents
Ethylene oxide (99.8% purity, Messer Griesheim Part No. 1284, or equiv.)
Acetaldedhyde (99.9%, Fluka Part No. 00070, or equiv.)

Polyethylene glycol 200 (PEG 200, Fluka Part no. 81150 with a specific gravity of 1.127 g/cm^3 or equiv.)
Deionized water (HPLC grade)
Defoamer (Agitan 281, Münzing Chemie GmbH, Heilbronn)

Procedure

Preparation of ethylene oxide standard stock solution

Add about 25 ml of PEG 200 into a 50 ml volumetric flask and accurately weigh the flask. Pass about 100 mg of gaseous ethylene oxide through polyethylene glycol 200 (PEG 200) and weigh. Calculate the mass of ethylene oxide absorbed by PEG 200 from the difference in weight. Dilute to volume with PEG 200 and weigh the flask. Calculate the amount of ethylene oxide per gram of solution (approximately 1.8 mg/g)

Preparation of ethylene oxide working standard solution-1

Add about 25 ml of PEG 200 into a 50 ml volumetric flask and weigh the flask. Add about 1 g of ethylene oxide stock solution to the volumetric flask and weigh. Dilute to volume with PEG 200. Calculate the concentration of ethylene oxide in the working standard solution from the weight (approximately 32 µg/g).

Preparation of ethylene oxide working standard solution-2

Add about 25 ml of PEG 200 into a 50 ml volumetric flask and weigh the flask. Add about 1 g of ethylene oxide working standard solution 1 to the volumetric flask and weigh. Dilute to volume with PEG 200. Calculate the concentration of ethylene oxide in the working standard solution from the weight (approximately 0.57 µg/g).

Preparation of acetaldehyde internal standard solution

Accurately weigh about 40 mg of acetaldehyde (to the nearest 0.1 mg), dissolve in water and dilute to 100 ml with water. Pipet 5 ml into a 50 ml volumetric flask and dilute to volume with water (approximately 40 µg/ml).

Preparation of sample solution

Accurately weigh about 0.5 g sample into a headspace vial containing 4.0 ml water and add 50 µl of defoamer. Add 1 ml of internal standard solution. Seal the vial and mix thoroughly.

System suitability test solution

Add 1 ml of the acetaldehyde solution and 0.1 ml of the ethylene oxide working solution in a headspace vial and add 4 ml of water. Seal the vial and mix thoroughly.

Blank solution

Add 50 µl defoaming agent to 1.0 ml of internal standard solution, and 4 ml of water and seal the vial.

Standard solution

Accurately weigh 0.1 g of ethylene oxide working standard solution (approximately 0.057 µg ethylene oxide), add 1.0 ml of internal standard, 4.0 ml water and add 50 µl of defoamer. Seal the vial and mix thoroughly.

Procedure

Chromatographic conditions

Column temperature: 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	5

Carrier gas: Helium
Column head pressure: 0.8 ml/min
Injection type: Splitless mode
Injection port temperature: 250°

Dynamic Headspace autosampler
Follow manufacturer's recommended conditions

Analysis

Run blank solution. Ethylene oxide peak shall be either absent or below limit of detection. Run system suitability standard solution.

System suitability

Retention time: acetaldehyde = about 5.8 min; ethylene oxide = about 6.2 min.
Resolution: Not less than 1.5 between acetaldehyde and ethylene oxide
Signal-to-noise: Not less than 10 determined from the ethylene oxide peak

Analyze standard solution and calculate the peak ratio between ethylene oxide and acetaldehyde peaks. Analyze the sample solution and calculate the peak area ratio between ethylene oxide and acetaldehyde peaks in sample solution.

Obtain the concentration of ethylene oxide in the sample from the peak area ratios of sample & internal standard and standard & internal standard, amount of standard and weight of sample taken in the headspace vial.

1,4-Dioxane

[Caution: 1,4-dioxane is used as a solvent in the method for the determination of ethylene glycol and diethylene glycol. Take the necessary precautions to ensure that cross-contamination does not occur.]

Principle

Determine by headspace gas chromatography as directed in Residual Solvents by Headspace Gas Chromatography (Vol. 4) using the following:

Reagents

1, 4 dioxane (99.8% Sigma Aldrich Part No. 296309, or equiv.)
Deionized water (HPLC grade)
N,*N*-dimethylacetamide (≥99.9% Fluka Part No. 44901, or equiv.)
Defoamer (Agitan 281, Münzing Chemie GmbH, Heilbronn)

Preparation of stock standard solution (500 ug/ml): Accurately weigh about 25 mg of 1,4-Dioxane into a 50 ml volumetric flask and make up to volume with water.

Preparation of working standard solution (50 ug/ml): Pipet 5 ml stock standard solution into a 50 ml volumetric flask and make up to volume with water.

System suitability standard
Accurately weigh 0.5 g of sample to a 10-ml pressure headspace vial. Add 1.0 ml of Working standard solution and 1.0 ml of *N*,*N*-dimethylacetamide, seal the vial, and mix. Inject 1 ml.

Standard in headspace vial
Pipet 1.0 ml of 1,4-Dioxane working standard solution into a 10 ml headspace vial and add 1.0 ml of *N*,*N*-dimethylacetamide, seal the vial, and mix. Inject 1 ml.

Sample in headspace vial
Accurately weigh 0.5 g of sample to a 10-ml pressure headspace vial. Add 1.0 ml of *N*,*N*-dimethylacetamide and 1.0 ml of water, seal the vial, and mix. Inject 1 ml.

System suitability
Run system suitability standard.
The signal-to-noise shall not be less than 5 determined from the 1,4-Dioxane peak, and the relative standard deviation is not more than 15% (6 analyses).

Calculation
Analyze the standard and sample solutions using the analytical conditions for Residual Solvents by Headspace Gas Chromatography as described in Vol. 4. Calculate the concentration of 1,4-Dioxane in the sample from the peak areas of standard, sample, and amount of standard and sample in the headspace vials.

Ethylene glycol and diethylene glycol

Principle
Determine by gas chromatography after derivatization with N-methyl-N-trimethylsilyl trifluoroacetamide (MSTFA), and following the standard addition method.

Equipment
Capillary gas chromatograph with autosampler, split injector and flame ionization detector (FID)
Fused silica capillary column (0.25-mm × 30-m) coated with 0.25 µm layer of 14% cyanopropylphenyl-86%-dimethylpolysiloxane, (DB-1701, J&W Scientific, or equiv.)

Reagents
1,4- Dioxane (Purity 99.0 %, minimum J.T. Baker, part. no. 9231, or equiv.)
Ethylene glycol (EG) (Purity 99.5%, e.g. Fluka, part. no. 03750, or equiv.)
Propylene glycol (PG) (Purity >99.5% (GC), e.g. ABCR, part. no. AB207089, or equiv.)
Diethylene glycol (DEG) (Purity 99.9%, Sigma-Aldrich, part. no.

03128, or equiv.)
N-Methyl-N-trimethylsilyl trifluoroacetamide (MSTFA) (Macherey & Nagel part. no. 701270.1100, or equiv.)

Procedure

[The method described involves the handling of hazardous substances. Attention is drawn to the handling of potentially dangerous materials]

Preparation of ethylene glycol and diethylene glycol standard solution

Accurately weigh about 50 mg each of ethylene glycol and diethylene glycol in a 25 ml volumetric flask and make to volume with 1,4-dioxane. Pipette 1 ml of solution into a 10 ml volumetric flask and make to volume with 1,4-dioxane. This yields a standard solution containing 0.2 mg/ml of ethylene glycol and 0.2 mg/ml diethylene glycol.

Preparation of ethylene glycol and propylene glycol standard solution

Accurately weigh about 100 mg each of ethylene glycol and propylene glycol in a 25 ml volumetric flask and make to volume with 1,4-dioxane. Pipette 1 ml of solution into a 10 ml volumetric flask and make to volume with 1,4-dioxane. This yields a standard solution containing 0.4 mg/ml of ethylene glycol and 0.4 mg/ml propylene glycol.

Preparation of stock sample solution

Accurately weigh about 500 mg of sample to the nearest 0.01 mg into a 10 ml volumetric flask, dissolve in 1,4-dioxane and make to volume.

Preparation of sample solution

Pipette 1 ml of stock sample solution into a reaction vial, add 1 ml of 1,4-dioxane, 2 ml of MSTFA and derivatize at 90° for 1 h. Inject and analyze 2 µl of the solution to determine an approximate amount of ethylene glycol and diethylene glycol present in the sample.

Preparation of system suitability solution A

Pipette 1 ml of ethylene glycol and diethylene glycol standard solution into a reaction vial, add 1 ml of 1,4-dioxane, 2 ml of MSTFA and derivatize at 90° for 1 h.

Preparation of system suitability solution B

Pipette 2 ml of ethylene glycol and propylene glycol standard solution into a reaction vial, add 2 ml of MSTFA and derivatize at 90° for 1 h.

Preparation of standard addition solutions

Pipette 0.2 ml, 0.3 ml, 0.4 ml, 0.5 ml and 0.6 ml of the ethylene glycol and diethylene glycol standard solution, respectively, into five separate reaction vials. Pipette 1 ml of stock sample solution into each reaction vial. Add 2 ml of MSTFA, and enough 1,4-dioxane to give a total volume of 4 ml in each reaction vial. Derivitize all solutions at 90° for 1 h.

Chromatographic system
Column temperature: See the temperature program table below.

Initial temperature (°)	Tempera-ture ramp (°/min)	Final tempe-rature (°)	Hold time at final tem-perature (min)
100	-	100	5
100	5	125	-
125	30	300	5
300	-	300	15

Injector temperature: 300°
Detector temperature: 300°
Carrier gas: Helium
Column inlet pressure: 8.7 psi
Split: 10 ml/min (adapted to the sensitivity of the system as necessary)
Septum purge: 3 ml/min
Injection volume: 2 µl

Ethylene glycol has a retention time of approximately 5.6 min
Propylene glycol has a retention time of approximately 5.8 min
Diethylene glycol has a retention time of approximately 11.9 min

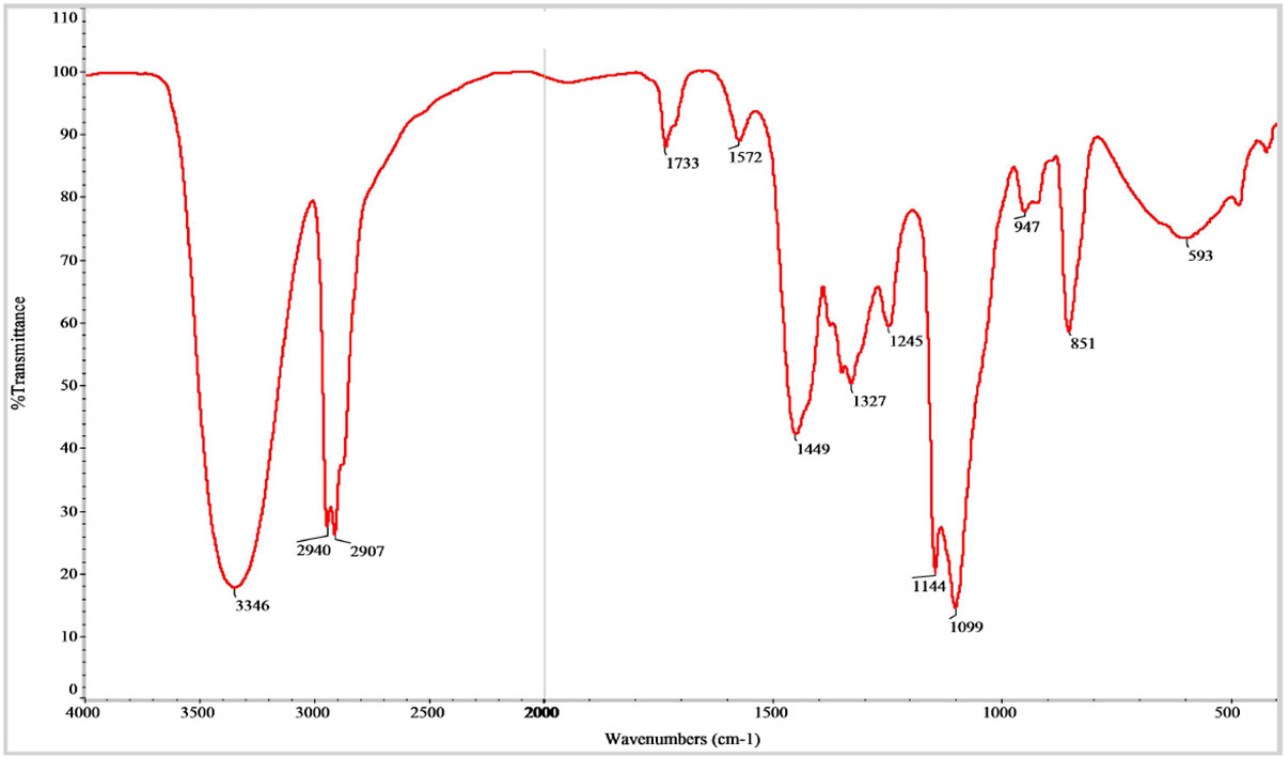
System suitability
Run Standard solution A. The system is suitable with a signal to noise ratio less than or equal to 10 for the signals of ethylene glycol and diethylene glycol

Run Standard solution B. The resolution shall not be less than 1.5 between the peaks of ethylene glycol and propylene glycol.

Analysis
Inject the derivatized standard addition solutions. Construct the standard curves by plotting the spiked mass (µg) of ethylene glycol or diethylene glycol on the x-axis versus the respective peak area on the y-axis, Deduce the amount of ethylene glycol or diethylene glycol in the sample (in the vial) from the x-intercept of the standard curve. Calculate the concentration in the sample from the amount of ethylene glycol or diethylene glycol determined from the standard curve, and the mass of sample in the vial.

Appendix

IR Spectrum for Polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft co-polymer



Acknowledgement

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