Polyethylene Glycol 3350

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Expert Committee	Complex Excipients

In accordance with the Rules and Procedures of the Council of Experts, the Complex Excipients Expert Committee has revised the Polyethylene Glycol 3350 monograph. The purpose for the revision is to widen the specification for formaldehyde in the *Limit of Formaldehyde and Acetaldehyde* from NMT 15 µg/g to NMT 30 µg/g to accommodate FDA-approved drug products.

The Polyethylene Glycol 3350 Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Hong Wang, Senior Manager, Science-Excipients (301-816-8351 or hw@usp.org).

This Notice was updated on November 25, 2020 to add the justification for the revision.

Revision Bulletin
Official: December 1, 2020

Polyethylene Glycol 3350

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-;
1,2-Ethanediol, homopolymer
[25322-68-3]; UNII: G2M7P15E5P.

DEFINITION

Polyethylene Glycol 3350 is an addition polymer of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups. The apparent weight-average molecular weight is 3015–3685 g/mol (Da). It contains NLT 97.0% and NMT 103.0% of polyethylene glycol 3350, calculated on the anhydrous basis. It may contain a suitable antioxidant.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197F. Use a thin film of test specimen, melted if necessary, in the range from 4000 to 650 cm^{-1}, when the measurement is performed by using 197F.
- **B. Chromatographic Identity**

  Analysis: Proceed as directed in the *Assay*.

  Acceptance criteria: The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY

- **Procedure**

  Mobile phase: 50 µg/mL of sodium azide in water

  Standard solution: 20 mg/mL of USP Polyethylene Glycol 3350 RS in *Mobile phase*

  Sample solution: 20 mg/mL of Polyethylene Glycol 3350 in *Mobile phase*

  Chromatographic system

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

  Mode: LC

  Detector: Differential refractive index

  Columns

  Guard: 6-mm × 4-cm; 6-µm packing L25

  Analytical: 7.8-mm × 30-cm; 6-µm packing L25

  Temperatures

  Detector: 35 ± 1°

  Column: 35 ± 1°

  Flow rate: 0.8 mL/min

  Injection volume: 20 µL

  System suitability

  Sample: *Standard solution*

  [Note—The retention time for polyethylene glycol 3350 is about 8.5 min.]

  Suitability requirements

  Relative standard deviation: NMT 1.5%

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of polyethylene glycol 3350 [$H(OCH_2CH_2)_nOH$] in the portion of Polyethylene Glycol 3350 taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Polyethylene Glycol 3350 RS in the *Standard solution* (mg/mL)

C_U = concentration of Polyethylene Glycol 3350 in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–103.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩

  Sample: 2 g

  Analysis: Proceed as directed, moistening the residue with 2 mL of sulfuric acid.

  Acceptance criteria: NMT 0.1%

- **Limit of Ethylene Oxide and Dioxane**

  Analysis: Proceed as directed in *Ethylene Oxide and Dioxane* ⟨228⟩*, Method II*.

  Acceptance criteria

  Ethylene oxide: NMT 1 µg/g

  Dioxane: NMT 10 µg/g

- **Limit of Ethylene Glycol and Diethylene Glycol**

  Mobile phase: 50 µg/mL of sodium azide in water

  Eluant: Water

  Standard stock solution: 10 mg/g of USP Diethylene Glycol RS and 10 mg/g of USP Ethylene Glycol RS in *Eluant*

  Standard solution: Transfer 0.1 g of *Standard stock solution* to a 100-mL volumetric flask. Dilute with water to volume. The *Standard solution* contains 0.01 mg/mL of USP Diethylene Glycol RS and 0.01 mg/mL of USP Ethylene Glycol RS.

  Sample solution: 10 mg/mL of Polyethylene Glycol 3350 in *Eluant*

  Chromatographic system

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

  Mode: LC

  Detector: Differential refractive index

  Column: 7.8-mm × 30-cm; 7-µm packing L89, 125-Å pore size

  Temperatures

  Detector: 35 ± 1°

  Column: 35 ± 1°

  Flow rate: 0.5 mL/min

  Injection volume: 100 µL

  Run time: 30 min

  System suitability

  Sample: *Standard solution*

  [Note—The relative retention times for diethylene glycol and ethylene glycol are 1.0 and 1.1, respectively.]

  Suitability requirements

  Resolution: NLT 0.9 between diethylene glycol and ethylene glycol

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of diethylene glycol (or ethylene glycol) in the portion of Polyethylene Glycol 3350 taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of diethylene glycol (or ethylene glycol) from the *Sample solution*

r_S = peak response of diethylene glycol (or ethylene glycol) from the *Standard solution*

C_S = concentration of USP Diethylene Glycol RS (or USP Ethylene Glycol RS) in the *Standard solution* (mg/mL)

C_U = concentration of Polyethylene Glycol 3350 in the *Sample solution* (mg/mL)

Acceptance criteria

Ethylene glycol: NMT 0.062%

Sum of diethylene glycol and ethylene glycol: NMT 0.2%

Change to read:

• **Limit of Formaldehyde and Acetaldehyde**

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time[a] (min)	Solution A (%)	Solution B (%)
0	50	50
11	0	100

[a] The equilibration time is 5 min.

[Note—Use amber containers and amber autosampler vials.]

2,4-DNPH solution: Transfer 250 mg of 2,4-dinitrophenylhydrazine (2,4-DNPH) to a 50-mL volumetric flask, add 20.0 mL of acetonitrile, and swirl to mix. Add 3.0 mL of hydrochloric acid to the flask, and swirl to mix. Sonicate until all solids are dissolved, and dilute with acetonitrile to volume.

Formaldehyde-2,4-DNPH solution: 100 µg/mL of aldehyde equivalent in acetonitrile[1]

Acetaldehyde-2,4-DNPH solution: 1000 µg/mL of aldehyde equivalent in acetonitrile[2]

Formaldehyde stock solution: Transfer 500 µL of *Formaldehyde-2,4-DNPH solution* to a 10-mL volumetric flask. Dilute with acetonitrile to volume. The formaldehyde concentration is 5.0 µg/mL.

Acetaldehyde stock solution: Transfer 500 µL of *Acetaldehyde-2,4-DNPH solution* to a 10-mL volumetric flask. Dilute with acetonitrile to volume. The acetaldehyde concentration is 50.0 µg/mL.

Standard solution: Transfer 1.5 mL of *Formaldehyde stock solution* and 1.2 mL of *Acetaldehyde stock solution* to a 10-mL volumetric flask. Dilute with acetonitrile to volume, and mix well. The concentrations of formaldehyde and acetaldehyde are 0.75 and 6.0 µg/mL, respectively.

Sample solution: Transfer 0.5 g of Polyethylene Glycol 3350 to a 10-mL volumetric flask. Add 1.0 mL of acetonitrile to the flask, and swirl to dissolve the sample. Add 2.0 mL of *2,4-DNPH solution* to the flask, and swirl to mix. Allow the solution to react for 15 min, then dilute with acetonitrile to volume.

Chromatographic system

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

Mode: LC

Detector: UV 360 nm

Column: 3.0-mm × 15-cm; 3.5-µm packing L7, 80-Å pore size

Column temperature: 30 ± 1°

Flow rate: 0.65 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for formaldehyde and acetaldehyde are 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 2.0 between formaldehyde and acetaldehyde

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the content of formaldehyde (or acetaldehyde), in µg/g, in the portion of Polyethylene Glycol 3350 taken:

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

r_U = peak response of formaldehyde (or acetaldehyde) from the *Sample solution*

r_S = peak response of formaldehyde (or acetaldehyde) from the *Standard solution*

C_S = concentration of formaldehyde (or acetaldehyde) in the *Standard solution* (µg/mL)

C_U = concentration of Polyethylene Glycol 3350 in the *Sample solution* (g/mL)

Acceptance criteria

Formaldehyde: NMT ▲30 µg/g▲ (RB 1-Dec-2020)

Sum of formaldehyde and acetaldehyde: NMT 200 µg/g

SPECIFIC TESTS

- **APPARENT WEIGHT-AVERAGE MOLECULAR WEIGHT AND POLYDISPERSITY**

Mobile phase: Water

Standard solutions: Prepare 1.0 mg/mL each of five polyethylene glycol standards with molecular weights of 1000, 2000, 3000, 4000, and 6000 Daltons (g/mol) in *Mobile phase* separately in five individual flasks. Pass a portion of each solution through a 0.45-µm polytetrafluoroethylene (PTFE) syringe filter.[3] Discard the first 2 mL, and transfer the solution for analysis.

Sample solution: 1.0 mg/mL of Polyethylene Glycol 3350 in *Mobile phase.* Pass a portion of the solution through a 0.45-µm PTFE syringe filter.[3] Discard the first 2 mL, and transfer the solution for analysis.

Chromatographic system

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

Mode: LC

Detector: Differential refractive index

Column: 7.8-mm × 30-cm; 6-µm packing L37

Temperatures

Detector: 35 ± 1°

Column: 35 ± 1°

Flow rate: 0.8 mL/min

Injection volume: 10 µL

Run time: 18 min

Analysis

Samples: *Standard solutions* and *Sample solution*

Separately inject equal volumes of the *Standard solutions* and the *Sample solution* into the chromatograph, record the chromatograms, and determine the elution peak maxima and the corresponding retention times for the five polyethylene glycol standards.

Calibration curve: Plot the retention times on the *x*-axis against the log M_P (M_P: peak molecular weights) on the *y*-axis for the peaks from the polyethylene glycol standard to generate a calibration curve using suitable gel permeation chromatography or size exclusion chromatography (GPC/SEC) software.

Calculations: Compute the data using the same GPC/SEC software, and determine the number- and weight-average molecular weights, M_N and M_W, in g/mol (Da), respectively, for the chromatogram of the *Sample solution*.

Calculate the polydispersity for Polyethylene Glycol 3350:

$$\text{Result} = M_W/M_N$$

M_W = weight-average molecular weight from the *Sample solution* (g/mol)

M_N = number-average molecular weight from the *Sample solution* (g/mol)

Acceptance criteria: The value of apparent weight-average molecular weight is 3015–3685 g/mol. Polydispersity is 90%–110% of the value stated on the label or within the range indicated on the label.

- **Hydroxyl Value**

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: Carefully introduce 25.0 mL of *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add 12.0 g of Polyethylene Glycol 3350. 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 60 min, 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 hydroxyl value:

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

M_r = molecular weight of potassium hydroxide, 56.11

V_B = volume of 0.5 N sodium hydroxide consumed in the blank test (mL)

V_S = volume of 0.5 N sodium hydroxide consumed in the actual test (mL)

N = exact normality of the sodium hydroxide solution

W = weight of Polyethylene Glycol 3350 taken for the test (g)

Acceptance criteria: 30–38

- **Acidity and Alkalinity**

Sample solution: Dissolve 5.0 g of Polyethylene Glycol 3350 in 100 mL of carbon dioxide-free water.

Analysis: Add 0.3 mL of a saturated solution of potassium chloride into the *Sample solution*. The test solution should be maintained at 25 ± 2° during the measurement. Measure the pH following *pH* ⟨791⟩.

Acceptance criteria: 4.5–7.5

- **Water Determination** ⟨921⟩, *Method I*
  Sample: 2.0 g
  Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from direct sunlight. Avoid exposure to excessive heat.
- **Labeling:** Label it to indicate its polydispersity (M_W/M_N) or its polydispersity range. Label it to indicate the name and amount of any added antioxidant.
- **USP Reference Standards** ⟨11⟩
  USP Diethylene Glycol RS
  USP Ethylene Glycol RS
  USP Polyethylene Glycol 3350 RS

Polyethylene Glycol 3350 —*see Polyethylene Glycol 3350 General Monographs*

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[1] Available from Sigma-Aldrich Corporation, or equivalent.

[2] Available from Sigma-Aldrich Corporation, or equivalent.

[3] Millipore® Millex® LCR HPLC syringe filters with hydrophilic PTFE membrane is suitable, or any other equivalent filter.

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