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Add the following:

▲⟨313⟩ MOLECULAR WEIGHT AND POLYMER CHAIN LENGTH DETERMINATION FOR POLYPROPYLENE GLYCOL FATTY ETHERS

Average molecular weight, polydispersity, and average polymer chain length are critical properties in understanding and control of excipient composition and variability during formulation development, manufacturing, and testing of polymeric excipients. The following gel permeation chromatography (GPC)/size exclusion chromatography (SEC) and nuclear magnetic resonance (NMR) spectroscopy procedures are used to determine average molecular weight, polydispersity, and average polymer chain length for polypropylene glycol fatty ethers. These procedures are suitable for the following substances:

- Polypropylene Glycol 11 Stearyl Ether
- Polypropylene Glycol 15 Stearyl Ether

METHOD 1: APPARENT WEIGHT-AVERAGE MOLECULAR WEIGHT AND POLYDISPERSITY

Mobile phase: Tetrahydrofuran. [Note—Filter the solvent using a polytetrafluoroethylene (PTFE) filter of 0.45-µm pore size if necessary.]

Standard solutions: Prepare 1.0 mg/mL each of at least 5 polypropylene glycol (PPG) standards with peak molecular weights ranging from approximately 70–4500 Da (g/mol)[1] in *Mobile phase* separately.

System suitability solution: 1.0 mg/mL of PPG standard with a peak molecular weight of approximately 1000 Da (g/mol)[1] in *Mobile phase*

Sample solution: 1.0 mg/mL of the test substance in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: Refractive index

Columns: Two 7.5-mm × 30-cm; 3-µm packing L21 columns in series

Temperatures

Detector: 30°

Column: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

Run time: 25 min

System suitability

Samples: *Standard solutions* and *System suitability solution*

Calibration curve: Plot the retention times on the *x* axis against the log M_p (M_p: peak molecular weight) on the *y* axis for the PPG peaks from the *Standard solutions* to generate a calibration curve using suitable GPC/SEC software. The correlation coefficient for the calibration curve is NLT 0.99.

Determine weight-average molecular weights, M_w, in g/mol (Da), from the chromatograms of the *System suitability solution*.

Suitability requirements

Relative standard deviation: NMT 5% for determined weight-average molecular weights of the PPG standard from 6 replicates, *System suitability solution*

Analysis

Samples: *Standard solutions* and *Sample solution*

Compute the data using the same GPC/SEC software from the chromatograms of the *Standard solutions* and *Sample solution* and determine the number- and weight-average molecular weights, M_n and M_w, in g/mol (Da), respectively, for the tested substance.

Calculate the polydispersity for the tested substance:

$$\text{Result} = M_w/M_n$$

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

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

METHOD 2: AVERAGE POLYMER LENGTH

Diluent: Deuterated chloroform containing 0.03% (v/v) tetramethylsilane[2]

Sample solution: Weigh about 100 mg of the tested substance. Dissolve it in 0.6 mL of *Diluent*.

Instrumental conditions

Mode: An NMR spectrometer that is capable of performing quantitative analysis (see *Nuclear Magnetic Resonance Spectroscopy ⟨761⟩, Qualitative and Quantitative NMR Analysis, Quantitative Applications*)

Flip angle: 90°

Analysis: Place the tube in the NMR spectrometer, and record the NMR spectrum. Integrate the peak areas from 0.6–1.8 ppm (A_1) and from 2.8–4.2 ppm (A_2).

The following are the equations for the total number of protons in the two regions (N_1 and N_2):

$$N_1 = N_{N1} + N_{N2} \times n$$

N_1 = total number of protons in the region of 0.6–1.8 ppm

N_{N1} = total number of protons in the fatty alcohol residual group (stearyl group for the two excipients currently listed in the chapter) not activated by oxygen, 35

N_{N2} = number of protons not activated by oxygen in each oxypropylene unit, 3

n = number of oxypropylene units per molecule

$$N_2 = N_{A1} + N_{A2} \times n$$

N_2 = total number of protons in the region of 2.8–4.2 ppm

N_{A1} = total number of oxygen activated protons not included in the oxypropylene unit, 3

N_{A2} = number of oxygen activated protons in each oxypropylene unit, 3

n = number of oxypropylene units per molecule

The areas in the two regions (A_1 and A_2) are correlated to the total number of protons in the regions (N_1 and N_2) as in the following equation:

$$A_2/A_1 = N_2/N_1$$

Calculate the number of oxypropylene units per molecule (n):

$$n = (N_{N1} \times A_2 - N_{A1} \times A_1)/(N_{A2} \times A_1 - N_{N2} \times A_2)$$

N_{N1} = total number of protons in the fatty alcohol residual group (stearyl group for the two excipients currently listed in the chapter) not activated by oxygen, 35

A_2 = area from 2.8–4.2 ppm by integration

N_{A1} = total number of oxygen activated protons not included in the oxypropylene unit, 3

A_1 = area from 0.6–1.8 ppm by integration

N_{A2} = number of oxygen activated protons in each oxypropylene unit, 3

N_{N2} = number of protons not activated by oxygen in each oxypropylene unit, 3▲ (USP 1-Aug-2023)

[1] A PPG standard kit from PSS (Polymer Standards Service; part number PSS-ppgkit) was used. The kit contained a total of 7 PPG standards with the peak molecular weight (M_P) range of approximately 70–4500 Da (g/mol). The PPG standard with an M_P of approximately 1000 Da (g/mol) was used for the *System suitability solution* preparation. An equivalent standard kit can also be used.

[2] The reagent from Sigma Aldrich (product #225789) was used. An equivalent reagent can also be used.

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

Topic/Question	Contact	Expert Committee
<313> MOLECULAR WEIGHT AND POLYMER CHAIN LENGTH DETERMINATION FOR POLYPROPYLENE GLYCOL FATTY ETHERS	Documentary Standards Support	ETM2020 Excipients Test Methods

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