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Add the following:

^⟨314⟩ MOLECULAR WEIGHT DETERMINATION FOR COPOLYMERS CONTAINING ALKYL METHACRYLATE OR ALKYL ACRYLATE

Average molecular weight and polydispersity 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) procedures are used to determine the average molecular weight and polydispersity for copolymers containing alkyl methacrylate or alkyl acrylate. The procedure is suitable for the following substances:

- Methacrylic Acid and Methyl Methacrylate Copolymer including Methacrylic Acid and Methyl Methacrylate Copolymer (1:1) and Methacrylic Acid and Methyl Methacrylate Copolymer (1:2)
- Methacrylic Acid and Ethyl Acrylate Copolymer
- Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion

APPARENT WEIGHT-AVERAGE MOLECULAR WEIGHT AND POLYDISPERSITY

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

Standard solutions: Prepare 1.0 mg/mL each of at least 7 poly(methyl methacrylate) (PMMA) standards with peak molecular weights ranging from approximately 600–2,000,000 Da (g/mol)¹ in *Mobile phase* separately.

Pass each solution using a suitable syringe compatible with [tetrahydrofuran](#) through a suitable filter of 1- μ m pore size into a high-performance liquid chromatography (HPLC) vial with the first 1–2 mL discarded before analysis.²

System suitability solution: 1.0 mg/mL of a PMMA standard with a peak molecular weight of approximately 190,000 Da (g/mol)¹ in *Mobile phase*. Pass the solution using a suitable syringe compatible with [tetrahydrofuran](#) through a suitable filter of 1- μ m pore size into an HPLC vial with the first 1–2 mL discarded before analysis.²

Sample solution: 1.0 mg/mL of the test substance in *Mobile phase* for a sample in solid form; 1.0 mg/mL equivalent to the corresponding solid form substance in *Mobile phase* for a sample in dispersion form. [NOTE—A sample in dispersion form can be dissolved in *Mobile phase* directly (without any pretreatment).] Pass the solution using a suitable syringe compatible with [tetrahydrofuran](#) through a suitable filter of 1- μ m pore size into an HPLC vial with the first 1–2 mL discarded before analysis.²

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: Refractive index

Columns: One suitable guard column³ and two 7.5-mm \times 30-cm; 5- μ m packing [L128](#) columns in series

Temperatures

Detector: 30°

Column: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 μ L

Run time: 30 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 PMMA 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* using the GPC/SEC software.

Suitability requirements

Relative standard deviation: NMT 10% for determined weight-average molecular weights of the PMMA 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)

▲ (USP 1-Dec-2023)

- ¹ A poly(methyl methacrylate) (PMMA) standard kit from PSS (Polymer Standards Service; part number PSS-mmkith) was used. The kit contained a total of 12 PMMA standards with the peak molecular weight (M_p) range that covers the region of approximately 600–2,000,000 Da (g/mol). The PMMA standard with an M_p of approximately 190,000 Da (g/mol) was used for the *System suitability solution* preparation. An equivalent standard kit can also be used.
- ² A glass syringe and a PTFE filter were used. An equivalent syringe and an equivalent filter can also be used.
- ³ A 5- μ m, 7.5-mm \times 5-cm Agilent PLgel Mixed guard column (part # PL1110-1520) was used. An equivalent guard column can also be used.

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
<314> MOLECULAR WEIGHT DETERMINATION FOR COPOLYMERS CONTAINING ALKYL METHACRYLATE OR ALKYL ACRYLATE	Documentary Standards Support	ETM2020 Excipients Test Methods

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