Characterization of phosphorylcholine-linked methacrylate polymer 1036 (PC1036)

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Statement of Purpose:

Poly (2-(methacryloyloxyethyl)-2'-(trimethylammoniumethyl) phosphate, inner salt)-co-(lauryl methacrylate)-co-(2-hydroxypropylmethacrylate)-co-(3-Trimethoxysilyl) propylmethacrylate, PC1036, is a "complex" polyelectrolyte. PC1036 is currently used on the Endeavor® drug eluting stent, therefore physical characterization of PC1036 is of interest. Previous attempts have not been successful due to complications such as: (1) PC1036 having four monomer units with diverse functionalities, Nuclear Magnetic Resonance (NMR) H^1 spectrum failed to give its chemical composition; (2) for molecular weight determination, one of the monomers of PC1036 has a high affinity to Gel Permeation Chromatography (GPC) column packings; and (3) the glass transition of the crosslinked PC1036 is very weak. This research has surmounted these troubles and led to characterization methods for this polymer.

Methods:

Size separation of PC1036 polymer was achieved by using co-solvents in GPC. Coupled with multi-angle light scattering detector (MALS), absolute molecular weight and polydispersity of the PC1036 were characterized successfully. GPC-Light Scattering equipment and experiment conditions:

Chromatograph system: Agilent 1100
Detectors: Wyatt Optilab rEX, Wyatt Dawn Heleos
GPC Column: Phenomenex Phenogel, 5u, 10-4Å, 300 x 7.80 mm
Guard Column: Phenomenex Phenogel, 5u, Linear Mixed, 50 x 7.80 mm
Mobile phase and the solvent: 40:60 EtOH:THF
Flow rate: 1 mL/min
Injection Volume: 100 uL
Nominal polymer concentration in Solution: 1%
Column Temperature: Room temperature

Modern NMR was performed on highly concentrated solutions of PC1036. The carbon spectra were acquired with 90° pulse length and 12 s relaxation delay (The ^{13}C spin-lattice relaxation times (T_1) was assumed less than 2 s). The ^1H decoupling was on during acquisition time and off during relaxation delay in order to eliminate Nuclear Overhauser Effect (NOE) for quantitative carbon NMR. All spectra were recorded at 30°C and carbon chemical shifts were referenced to the solvent signal of CD_3OD at 49.0 ppm. At least 5000 transits were acquired for each sample and the spectra were processed with 5 Hz line broadening and baseline correction using a first to twentieth order polynomial fitting of pre-defined baseline regions. The integration values of distinguished peaks from each monomer were used to calculate the monomer ratios. ^{13}C NMR results enabled characterization of the mole percentage of each of the polymer's four building units for multiple batches with high accuracy.

The glass transition temperatures (Tg) of linear and crosslinked PC1036 polymers were characterized by Differential Scanning Calorimetry (DSC) and Dynamic Mechanical Analysis (DMA), respectively. The sample size of the DSC experiments was about 10 mg. Both hermetically sealed and standard pans were used. The DSC thermal cycles were -90°C to 140°C to -90°C, and then to 250°C at a rate of 20°C/min. For DMA, a TA Q800 equipped with film tension clamp was used. Samples were cut to about 4mm X 5 mm X 1.5mm. The DMA conditions were a temperature ramp from -20 to 200°C at 3 ºC/min with oscillations of 5 μm amplitude at 1 Hz. The water content of the polymer was determined by Thermal Gravimetric Analysis (TGA) for each sample tested.

Results:

Through ^{13}C NMR studies of each the monomers, the characteristic chemical shift for the carbon atoms on each monomer molecule to be assigned. The signal intensity is directly proportional to the number of nuclei in the NMR sample. In the ^{13}C NMR spectrum of PC1036 polymer, the specific signals associated with the four different monomers in PC1036 were well resolved allowing direct calculation of the relative monomer fractions from the integrated signal intensity. The results from the study of 5 batches validated the ability of the NMR method to determine the molar percentage of the four-monomer units in PC1036. The results were as follows:
26.0 % of 2-(methacryloyloxyethyl)-2'-(trimethylammoniumethyl) phosphate, inner salt (PC);
50% of Lauryl methacrylate (LA);
19.1% of 2-Hydroxypropylmethacrylate (HPMA);
and 4.9% of Trimethoxysilyl propylmethacrylate (SMT).
The molar ratios differ from the manufacturer's specification by +3%, 3%, -6%, and 0%, respectively. GPC-MALS results showed the weight average molecular weight of PC1036 (6 batches) to be 113,250 Dalton, and with a polydispersity of 1.62. The relative standard deviations were about 5% and 4%, respectively. The Tg of linear PC1036 (which contained approximately 3% water) obtained by DSC measurements is 50˚C. DSC was not capable of measuring the Tg of the crosslinked PC1036 (which contained approximately 1.3% water) due to relatively weak signals seen with these samples. The Tg's of crosslinked PC1036 specified by the maximum value of tan δ and loss moduli from DMA analysis were 95˚C and 62˚C, respectively.

Conclusions:

Methods for NMR, GPC-MALS, DSC, and DMA were developed for analysis of Phosphorylcholine Methacrylate polymer PC1036. These methods enabled successful characterization of multiple batches of PC1036.

References:

1. Andrew L. Lewis et al. Biomaterials 21 (2000), 1847-1859.
2. E.F. Murphy et al, Macromolecules 2000, 33, 4545-4554