Assessing Q1/Q2 sameness of polyethylene glycol star polymers as polymeric excipients in dexamethasone ophthalmic inserts

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Background and Purpose

DEXTENZA (dexamethasone ophthalmic insert, NDA 208742), was approved on 11/30/2018. The product, used for treating ocular inflammation and pain following ophthalmic surgery, is a 3 mm cylindrical-shaped intracanalicular insert comprised of a resorbable polyethylene glycol (PEG)-based hydrogel. The manufacture of the product involves the entrapment of insoluble dexamethasone drug substance as a physical mixture with other polymeric excipients. Critically, a 4-arm PEG star is used, enabling a solution-phase crosslinking reaction to form the hydrogel network. As this excipient controls both the physical/mechanical properties (e.g., swelling) and the rate of release via aqueous perfusion to the entrapped active pharmaceutical ingredient, assessment of polymeric excipient sameness may be critical for equivalent performance.

In this work, we delve into in vitro characterization of the excipients used in the implant manufacturing to address challenges in determining qualitative (Q1) and quantitative (Q2) sameness. Here we evaluate some proposed properties of the polymeric excipient, including molecular weight, end-group functionalization, and number of arms, which may impact both manufacturing and end-product performance. Addressing the question of methodologies for determination of inactive ingredient sameness for the polymeric excipient, especially between vendors and "grades", may be an important aspect for industrial stakeholders and regulatory reviewers considering development of generic polymeric implants.

Materials and Methods

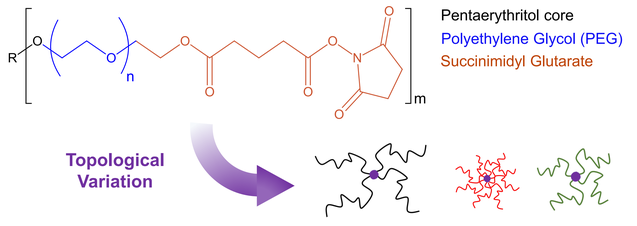

Table 1: Sample information from manufacturer Certificate of Analyses (CoAs). Purity was assessed by HPLC, molar mass (M_n) by MALDI-TOF, and polydispersity index (PDI) by SEC

Company	# of arms	Purity (%)	Molecular Weight (Da)	PDI	Nomenclature for Study
JenKem	4	95.6	40,748	1.04	J4a-40k
JenKem	8	99.4	20,700	1.04	J8a-20k
JenKem	4	92.2	20,937	1.02	J4a-20k
Biopharma PEG*	4	≥ 95	20,620	-	B4a-20k
Creative PEGWorks	4	-	22,000	1.02-1.05	C4a-20k

Polymer Properties	Analytical Techniques
End-group functionalization	FTIR and ^{1}H NMR
Molecular weight (M_w, M_n)	SEC-MALS-dRI-viscometry MALDI-TOF MS
Hydrodynamic size (R_h)	SEC-MALS-dRI-viscometry Batch-DLS

FTIR: Fourier transform infrared spectroscopy
NMR: nuclear magnetic resonance spectroscopy
SEC: size exclusion chromatography
MALS: multiangle light scattering
dRI: differential refractive index
DLS: dynamic light scattering
MALDI-TOF MS: matrix-assisted laser desorption ionization- time of flight mass spectrometry

Analysis of End-group Functionalization

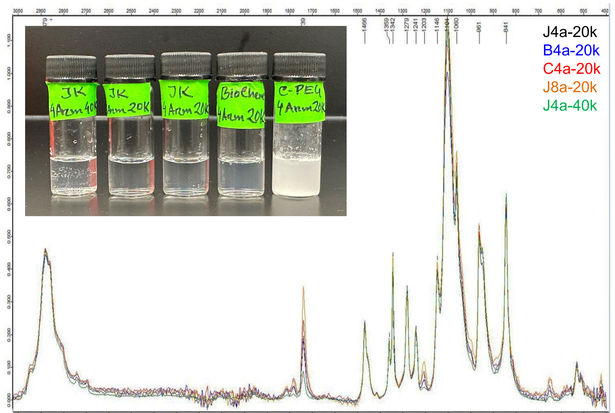

Figure 1: Overlay of FTIR spectra for each PEG polymer. The inset photo shows the polymers prepared in water to qualitatively examine the solubility. The C4a-20k shows differences in solubility and increased C=O content at 1738 cm^{-1} which can be related to possible impurities.

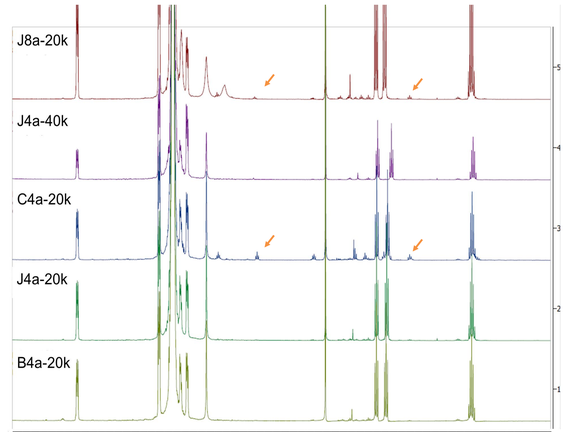

Figure 2: ^{1}H NMR spectra overlay of all five polymers. While all polymers showed presence of NHS terminal groups,C4a-20k showed similar impurities observed in FTIR as evident in the baseline between 2.3 and 3.4 ppm.

Determination of PEG Molecular Weight and Branching

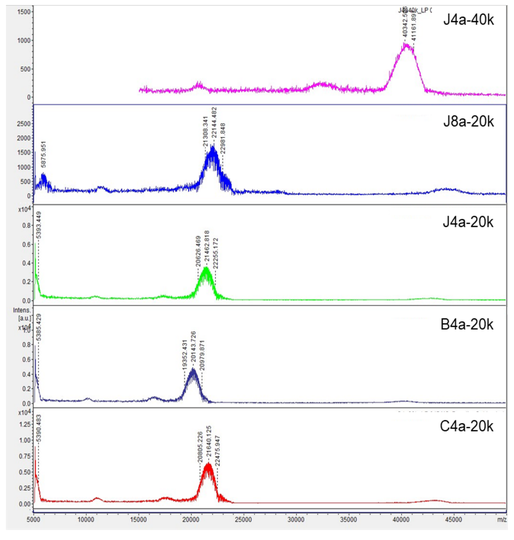

Figure 3: MALDI-TOF MS spectra for all samples using a matrix of 2,5-dihydroxybenzoic acid (DHB) with sodium chloride as the cationization agent. Similar molar masses (M_n) to those provided by the manufacturer CoAs were observed.

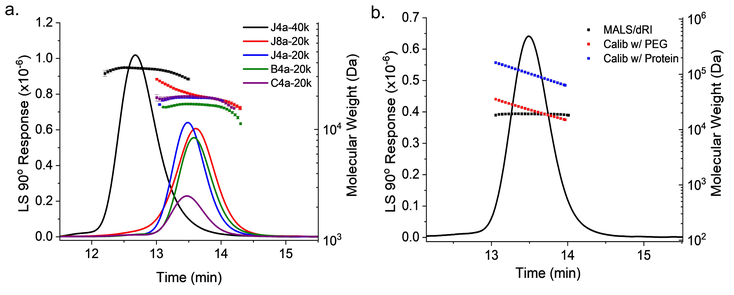

Figure 4: (a) Molecular weight distribution across each peak for PEG star polymers. Chromatograms for each sample has been signal-averaged from triplicate measurements (n=3). The error bars included in the M_w distributions represent one standard deviation from the mean. (b) Examination of differences in magnitude for M_w distributions of the J4a-20k sample when using an absolute value from MALS and dRI or from calibration curves using linear PEG standards or globular proteins.

Table 2: Branching ratio (g'), and the number of branch units per molecule for the star polymers using a drainage parameter of 1.0. These results are from triplicate data (n = 3) and error is one standard deviation from the mean.

Sample	Branching Ratio (g')	Branch units per molecule (Full Peak)	Branch units per molecule (Peak Max)
J4a-40k	0.78 ± 0.02	3.9 - 5.4	4.45 ± 0.06
J8a-20k	0.496 ± 0.001	7.3 - 13.8	8.51 ± 0.06
J4a-20k	0.816 ± 0.003	3.6 - 4.8	3.77 ± 0.06
B4a-20k	0.816 ± 0.003	3.1 – 4.7	3.73 ± 0.04
C4a-20k	0.807 ± 0.007	2.5 – 5.1	3.74 ± 0.04

Variability in Polymer Hydrodynamic Size

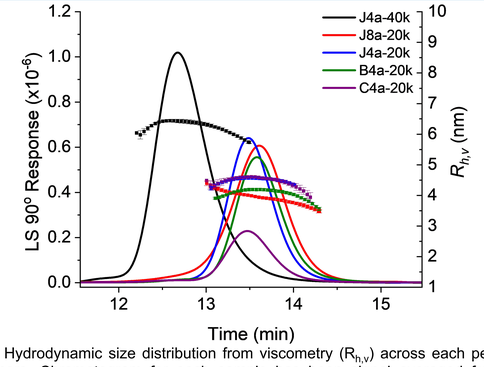

Figure 5: Hydrodynamic size distribution from viscometry ($R_{h,v}$) across each peak for PEG star polymers. Chromatogram for each sample has been signal averaged from triplicate measurements (n=3). The error bars in the $R_{h,v}$ represent one standard deviation from the mean.

Table 3: Hydrodynamic radius from viscometry ($R_{h,v}$) and two different batch-mode DLS ($R_{h\text{-}DLS}$) instruments: *Dynapro Plate Reader and ** Zetasizer Nano. The error bars in the $R_{h,v}$ represent one standard deviation from the mean (n=3).

Sample	$R_{h,v}$ (nm)	$R_{h\text{-}DLS}$ (nm)*	$R_{h\text{-}DLS}$ (nm)**
J4a-40k	6.37 ± 0.05	5.9 ± 0.1	5.76 ± 0.05
J8a-20k	4.10 ± 0.05	3.9 ± 0.1	4.56 ± 0.05
J4a-20k	4.53 ± 0.00	4.2 ± 0.1	4.52 ± 0.06
B4a-20k	4.33 ± 0.05	-	3.81 ± 0.02
C4a-20k	4.53 ± 0.05	4.5 ± 0.2	4.1 ± 0.2

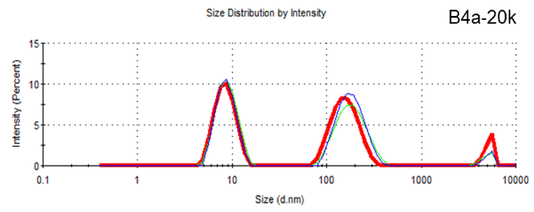

Figure 6: Triplicate measurements using batch DLS (ZetaSizer Nano) for the B4a-20k sample showing an unanticipated bimodal distribution. This multi-modal distribution was also observed for this sample using the plate reader DLS.

Conclusion

SEC with online MALS-Viscometry-dRI along with MALDI-TOF analyses showed similar molecular weights and polydispersity indices for samples compared to those listed on manufacturer CoAs. Star polymers with a lower degree of branching (4-arm) showed the anticipated larger hydrodynamic size and branching ratio compared to that of the 8-arm star polymer using online viscometry and were corroborated by batch DLS. Overall, the molecular weight results along with observed differences in the solubilization behavior of the polymers during sample preparation indicate the presence of qualitative differences between polymers sourced from different vendors. The impact of these qualitative and quantitative differences on manufacturing and product quality is the focus of ongoing investigational studies.

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